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Archives of Internal Medicine

VOL. 26 DECEMBER, 1920 No. 6

THE USE OF A HIGH FAT DIET IN THE TREATMENT OF DIABETES MELLITUS*

FIRST PAPER

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ANN ARBOR, MICH.

The treatment of diabetes mellitus has been very greatly improved in the recent past, owing to the work of Allen[1] and his colleagues. It has been shown by him that the urine of the severest diabetics can be made sugar free by sufficiently prolonged starvation and will remain sugar free if the total energy intake is kept sufficiently small.

It has been the general custom to make up the diet largely of protein, because of the undoubted desirability of omitting carbohydrates, and because of the almost universal fear of precipitating a dangerous acidosis by allowing more than a minimum of fat. This high protein, low fat, low carbohydrate diet, given in quantities sufficient to maintain metabolic needs, is accompanied by a glycosuria in the severe diabetics. In order to prevent glycosuria, it is necessary to restrict the total energy intake so much that inanition results. In other words, this leaves the physician the choice of one of two procedures. On the one hand, he may keep the patient sugar free, but in so doing, because of the low energy intake, he renders him unfit for the ordinary activities of life. On the other hand, if he aims to avoid this incapacity for his patient, he must expect him to continue to suffer from the effects of hypergylcemia.

It is evident that the two horns of the dilemma can be avoided if the diabetic can safely be given enough calories to maintain metabolic equilibrium, without producing hyperglycemia or acidosis.. Since carbohydrate cannot be used, and since protein is, as just pointed out, unsatisfactory, we have dared to ignore the belief concerning the danger of fat in the diet of diabetics, and have investigated in the clinic the effect of a diet whose energy comes largely from fat, to

* From the Department of Internal Medicine, Medical School, University of Michigan.

1. Allen, F. M.: Tr. A. Am. Phys. **32**:138, 1917; Am. J. M. Sc. **153**:313, 1917.

which is added sufficient protein to maintain nitrogen equilibrium and the minimal carbohydrate necessitated in making up a diet that a human being can eat over a long period of time.

For the purpose of studying this question, we have adopted a routine procedure. When a patient enters the clinic, he is placed on a diet containing from 900 to 1,000 calories, of which about 90 gm. is fat, 10 gm. is protein and 14 gm. is carbohydrate. After the patient has been sugar free for one or two weeks, his diet is increased to about 1,400 calories, of which 140 gm. is fat, 28 gm. is protein and from 15 to 20 gm. is carbohydrate. In the cases of small individuals this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1,800 calories, containing 170 gm. of fat, from 30 to 40 gm. of protein, and from 25 to 30 gm. carbohydrate. Further additions up to 2,500 calories may be made to suit individual cases.

In order to prove that our procedure is an improvement over the usual method, we must show, (1) that glycosuria is avoided in severe diabetics; (2), that this diet does not precipitate acidosis; (3), that nitrogen equilibrium is maintained, and (4), that the patients are able to lead at least a moderately active, comfortable life.

We have thus far had the opportunity of studying the effect of our method in the treatment of seventy-three cases of true diabetes mellitus. There has been no selection of cases—every patient entering the service has been placed on this regimen. The majority of these seventy-three cases have been of the severest type. This follows from the fact that the physicians of the state consider the University Hospital the court of last appeal, and send us those patients who do not respond to simple diabetic measures.

In spite of the fact that so many of our cases were of the severe type, we have succeeded in rendering and keeping every patient sugar free up to the time of discharge. The following case is an example of the response of a severe diabetic to our treatment.

REPORT OF CASE

Case 1 (No. 20-426).—A woman, aged 34 years, entered the clinic June 8 with a letter from her family physician in which he stated that he had been unable to render her urine free of sugar, even though he had starved her for nearly a week. She confirmed his story and said that she was so weak that she could hardly walk.

She was immediately placed on our first high fat diet, containing 900 calories. It was not until June 25, that the last trace of sugar disappeared from her urine. The ferric chlorid test became negative June 29. July 1, her diet was increased to 1,400 calories, of which 140 gm. were fat, and July 9 it was again increased to 1,800 calories, of which 170 gm. were fat. During her last week in the hospital, she took a walk after each meal and stated that she had

practically regained her normal strength. At no time after its first disappearance did glycosuria develop. She was discharged July 15 on the diet containing 1,800 calories, of which 170 gm. were fat, 40 gm. protein and 25 gm. were carbohydrate.

In order to show that the usual high protein diet is accompanied by glycosuria in these severe diabetics, we have submitted three of our patients, previously made sugar free by means of our diet containing 90 gm. of fat and 16 gm. of protein, to such a high protein diet. Each one of these individuals became glycosuric as a result of this change to a high protein diet and was again quickly made sugar free by a return to the original diet.

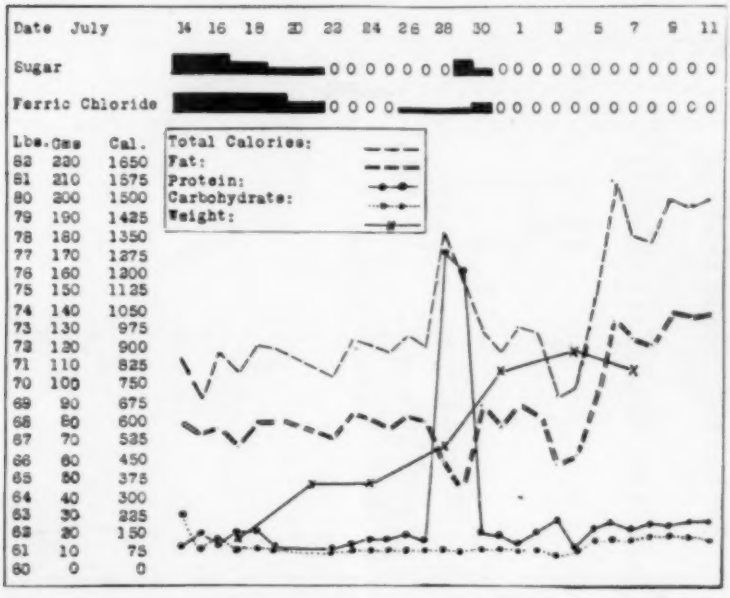

Fig. 1—Case 2 (20-475). Showing (1) disappearance of urinary sugar on high fat diet; (2) its reappearance on high protein diet; (3) its disappearance again on high fat diet and (4) its continued absence with increase of calories by addition of fat.

Case 2 (No. 20-475).—A woman, aged 33 years, who on a low carbohydrate high protein diet, had lost 40 pounds' weight in a year, entered the clinic July 14, weighing 62 pounds. On a diet of 18 gm. protein, 80 gm. fat and 14 gm. carbohydrate, totaling 900 calories, her urine became sugar free July 21, and remained so during the following week. On each of two days, July 28 and 29, she received 170 gm. protein, 55 gm. fat and 12 gm. carbohydrate, totaling 1,200 calories. July 30 she was returned to her former diet. The urine of July 29 and 30 contained, respectively, 11 and 3 gm. glucose. The urine of July 31 was sugar free. August 5, her diet was increased to 1,400

calories, with 25 gm. protein, 140 gm. fat and 20 gm. carbohydrate. On this diet her urine has remained sugar free. The data are presented graphically in Figure 1.

Case 3 (No. 20-461).—This patient was brought to the clinic July 2, 1920, on the verge of coma. He was confused, so weak that he could not stand, and showed the classic Kussmaul breathing. As a result of our first high fat diet (containing 90 gm. fat and 900 calories), sugar disappeared from his urine July 13. The acidosis disappeared on the same day. July 20, after having shown no sugar in his urine for a week, he was placed on a diet containing 900 calories, of which about 130 gm. were protein. His total calories were the same as on the high fat diet, and his carbohydrate intake was unchanged. His urine on the fourth and fifth day of this diet contained sugar. Clearly, the return of glycosuria in a patient previously sugar free on our high fat diet was due to the substitution of protein for fat.

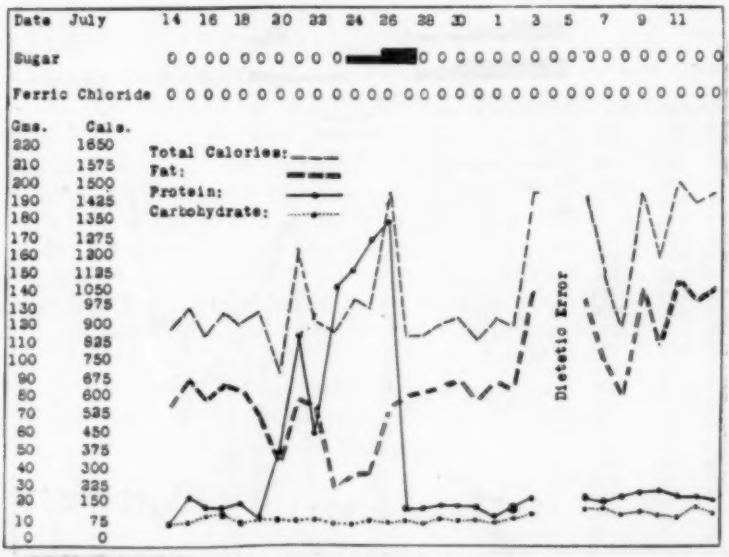

Fig. 2.—Case 3 (20-461). Showing (1) absence of urinary sugar on high fat diet; (2) its reappearance on high protein diet; (3) its disappearance on subsequent high fat diet and (4) its continued absence with increase of calories by addition of fat.

We felt it was highly desirable to feed this patient 1,500 calories in order to avoid inanition, provided, also, that this could be done without producing a return of the diabetic state. Accordingly we gave him the desired number of calories, made up in the usual way, largely of protein. The diet had the following composition: Total calories, 1,483; protein, 181 gm.; fat, 78 gm.; carbohydrate, 14 gm. His urine the next day contained 11.4 gm. sugar. Only one day of this diet was required to convince us that it was unsuitable, and he was returned to the original high fat diet. On the second day of this latter diet, his urine became sugar free, and remained so. August 1, his calories

were increased to 1,500, of which 150 gm. were fat, 30 gm. protein, and 20 gm. carbohydrate. He continued to remain sugar free, made a gain in weight (from 88 to 97 pounds) in two weeks, and was furnished slightly more than 0.66 gm. protein per kilogram of body weight. This diet, then, of 1,500 calories, containing 150 gm. fat, fulfilled our two specifications; first, that he remain sugar free, and second that he suffer no inanition. The data from August 13 to July 11, are presented graphically in Figure 2.

Case 4 (No. 20-427).—This man had had a severe diabetes which had never been treated systematically before his entrance to the hospital June 9. After four days of our fat diet, he became sugar free. July 26, after he had been sugar free for nine days on a diet of 28 gm. protein, 130 gm. fat, and 20 gm. carbohydrate, totaling 1,400 calories, he was given the same 1,400 calories, of which 185 gm. were protein, 50 gm. were fat and 12 gm. were carbohydrate. The urine of July 29 and 30 contained 6.4 and 7.2 gm. sugar, respectively. July 30 he was returned to the original 900 calories, high fat diet, and the next day his urine was sugar free. His diet was then increased according to our usual procedure, and he was still sugar free when he left the hospital.

All three of these patients demonstrated their inability to tolerate, without glycosuria, a diabetic diet of the ordinary type containing a relatively large amount of protein. Yet they readily and promptly responded to our high fat diet with a disappearance of urinary sugar. Two diets of the same number of calories, one rich in protein and the other rich in fat, produced a glycosuria in the first case and no glycosuria in the second. These experiments, coupled with the fact that we have yet to see a patient who does not become sugar free on our regimen, justify us in believing that patients who would continue to have a glycosuria on the standard high protein diet, containing sufficient calories to prevent inanition, may be expected to become and remain sugar free on a diet of the same number of calories of which nearly all are in the fat content.

Having in mind the prevailing fear of the use of fat in the diet of diabetics we were very much surprised to find, when fat is used, as we used it in the management of our seventy-three cases, that such fear is entirely ungrounded. In no case did a serious acidosis develop. It is true that four of these seventy-three patients died in the hospital, but none of these deaths was due to our diet. One patient entered the hospital with influenzal pneumonia. Another one was transferred from the surgical clinic suffering from a severe sepsis accompanying suppurative mastoid disease. Both of these patients died within twenty-four hours after their admission to the medical service. The third patient came to the hospital in coma and died ten hours after admission. The fourth patient refused to limit herself to the diet, and went into coma after eating a bag of oranges brought by a relative. None of these fatalities can, by any stretch of the imagination, be attributed to the high fat diet. In no case did the much feared fat produce any untoward symptoms.

Not only was this true, but unexpectedly enough, acidosis, even though marked, existing at entrance, invariably cleared up under our treatment. The following cases are examples of this beneficial effect on the acidosis.

Case 3 (No. 20-461) shows how the high fat diet may be attended by the gradual diminution and final disappearance of acidosis. This patient was brought to the hospital June 30 in a semicomatose condition, with the air hunger typical of extreme acidosis. An idea of the severity of the acidosis may be obtained from noting the fact that 157 gm. of sodium bicarbonate during the seventeen hours after his admission failed to make his urine neutral. July 2, when he had recovered from his stupor sufficiently to be able to eat, he was placed on our routine diet with its 90 gm. of fat daily. July 13, eleven days later, his urine was sugar free, and on the same day the ferric chlorid test on his urine became negative.

Case 2 (No. 20-475) shows well the simultaneous disappearance of sugar and ferric chlorid reaction from the urine of a severe diabetic, as a result of our high fat diet. The data are presented in Table 1.

TABLE 1.—Relation of Diet to Disappearance of Sugar and Acetone Bodies from Urine

Date	Urinary Sugar*	Ferric Chlorid Reaction
July 14 (entrance)	++++	++++
15	15.6	+++
16	22.0	++++
17 (part specimen)	0.0	++++
18	6.9	++++
19	1.0	++++
20	4.7	+++
21	4.1	++++
22	0.0	0
23	0.0	0

* Sugar is expressed in grams per twenty-four hours. Ferric chlorid ++++ means that the typical color reaction was still obtained after the urine had been diluted four times with equal volumes of water.

Case 4 (No. 20-427), a severe diabetic already described above, never showed more than a trace or "one plus" of ferric chlorid reaction in his urine.

Case 5 (No. 19-537).—The patient, a severe diabetic, 21 years old, ran the usual clinical course on our diet. The data are presented in Table 2.

The patient, who is Case 6 in this report, is being treated experimentally in the department of pediatrics, and his case is cited through the courtesy of Dr. D. M. Cowie. Because of the well known fact that diabetes in young children is especially severe and usually rapidly fatal, we consider this case of great value as evidence in support of the view that a high fat diet is not attended by dangerous acidosis.

TABLE 2.—Relation of Diet to Disappearance of Sugar and Acetone Bodies from Urine

Date, 1919	Urinary Sugar	Ferric Chlorid Test	Blood Sugar	Carbon Dioxid Tension of Alveolar Air
Nov. 22	++++	+	0.30	
24	+++	+		
25	+++	+		
26	++	+		
27	+	+	0.21	
28	++	+		
29	+	+	....	30.0
30	+	+	....	40.6
31	0	+		
Dec. 1	0	0		
2	0	0		
3	0	0	0.176	45.0
4	0	0		
5	0	0		
6	0	0		

Case 6 (No. 4923).—A boy, 7 years old, entered the hospital Oct. 15, 1919, complaining of increasing weakness and great loss of weight. The carbon dioxid tension of the alveolar air was 20 mm. mercury. The therapeutic result as regards glycosuria was not entirely satisfactory because the boy occasionally departed from his diet. The case does, however, show the inocuousness of a long continued high fat diet. The data during a period when the diet was characterized by its high fat content, are presented in Figure 3.

It is not necessary to describe more cases than these because those presented are typical and characteristic of the whole series. Even though we are repeating, we feel it necessary to point out again that none of the patients whom we treated by means of our high fat diet developed a severe acidosis. It is true, on the contrary, that the evidence of acidosis progressively decreased day by day until it had invariably become negligible.

No diet can be considered adequate in the treatment of diabetes unless it will maintain nitrogen balance. Our diet is comparatively low in protein, and is open to the possible criticism that it contains insufficient nitrogen. It has been shown by several observers, and notably by Hindhede,[2] that less than 0.66 gm. protein per kilogram of body weight, in the presence of sufficient calories from other sources, is more than enough to maintain nitrogen balance in healthy ordinarily active human beings. Our diet is constructed with this requirement in mind, and is so arranged that it contains at least 0.66 gm. protein per kilogram of body weight before the patient is discharged from the clinic.

But what is true for the normal man may not hold for the diabetic. It accordingly becomes necessary to determine the actual ratio between the nitrogen intake and nitrogen output of diabetics on our diet. This was done by the usual procedure. The intake was computed from

2. Hindhede: Skand. Arch. Physiol. **30**:97, 1913.

TABLE 3.—Case 19-444, Showing the Nitrogen Metabolism of a Diabetic Being Fed a High Fat Low Protein Diet*

Date	Urine Volume	Glucose Urine	Blood Sugar	Body Weight	Stool Weight	Intake					Output		
						Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Nitrogen Intake	Nitrogen Urine	Nitrogen Stool	Nitrogen Balance
9/ 5	3,300	+++	0.52	96.0	..	16.30	97.40	9.87	1,008				
9/ 6	3,525	+++	....	....	..	16.30	97.40	9.87	1,008				
9/ 8	2,110	+++	0.36	....	..	16.30	97.40	9.87	1,008				
9/10	2,950	+++	0.29	....	..	16.30	97.40	9.87	1,008				
9/12	2,880	+++	0.24	91.0	..	16.30	97.40	9.87	1,008				
9/15	2,700	++	0.20	....	..	16.30	97.40	9.87	1,008				
9/16†	.....	.....	....	....	..	.....	.....	...	.....				
9/17	?	+++	0.42	....	..	16.30	97.40	9.87	1,008				
9/18	3,000	+++	....	....	..	16.30	97.40	9.87	1,008				
9/21	3,100	+++	0.23	87.0	..	16.30	97.40	9.87	1,008				
9/22	2,900	0	....	....	..	16.30	97.40	9.87	1,008				
9/25	2,600	0	0.15	85.5	..	16.30	97.40	9.87	1,008				
9/30	2,500	0	....	85.5	..	24.87	141.42	9.89	1,458				
10/ 1	2,500	0	....	85.0	..	24.87	141.42	9.89	1,458				
10/ 2	2,250	0	0.16	85.0	..	24.87	141.42	9.89	1,458				
10/ 3	2,750	0	....	84.0	..	24.87	141.42	9.89	1,458				
10/ 4	1,510	0	....	84.5	..	24.87	141.42	9.89	1,458				
10/ 5	2,050	0	....	86.2	..	24.87	141.42	9.89	1,458				
10/ 6	2,085	0	....	86.0	..	24.87	141.42	9.89	1,458				
10/ 7	1,200	0	0.15	86.2	99	24.87	141.42	9.89	1,458	3.019	6.714	0.940	—3.675
10/12	2,565	0	0.13	88.5	..	36.82	192.87	9.87	1,981				
10/13	2,050	0	0.15	88.5	..	36.82	192.87	9.87	1,981				
10/14	2,900	0	....	88.0	..	36.82	192.87	9.87	1,981				
10/15	1,400	0	0.18	88.0	..	36.82	192.87	9.87	1,981				
10/16	2,600	0	....	88.0	..	36.82	192.87	9.87	1,981				
10/17	1,750	0	....	87.0	92	36.82	192.87	9.87	1,981	5.891	5.375	0.929	—0.929
10/22	1,055	0	....	89.5	..	36.82	192.87	9.87	1,981				
10/23	1,115	0	....	90.0	..	36.82	192.87	9.87	1,981				
10/24	1,430	0	0.15	92.5	39	36.82	192.87	9.87	1,981	5.891	4.855	0.913	+0.123
10/26	1,430	0	....	93.5	..	36.82	166.20	9.87	1,682				
10/27	1,535	0	....	94.0	..	36.82	166.20	9.87	1,682				
10/28	1,500	0	....	94.5	..	36.82	166.20	9.87	1,682				
10/29	2,000	0	....	94.5	..	36.82	166.20	9.87	1,682				
10/30	1,708	0	....	94.5	..	36.82	166.20	9.87	1,682				
10/31	2,470	0	0.15	94.2	42	36.82	166.20	9.87	1,682	5.891	2.433	0.421	+3.037
11/ 1	2,080	0	....	94.5	..	36.82	166.20	9.87	1,682				
11/ 2	2,430	0	....	93.0	..	36.82	166.20	9.87	1,682				
11/ 3	1,700	0	....	93.0	..	36.82	166.20	9.87	1,682				
11/ 4	1,850	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/ 5	2,120	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/ 6	1,800	0	....	92.0	..	28.08	162.80	9.87	1,604				
11/ 7	1,920	0	0.15	91.5	35.5	28.08	162.80	9.87	1,604	5.092	2.965	0.455	+1.672
11/11	2,235	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/12	2,305	0	....	92.2	..	28.08	162.80	9.87	1,604				
11/13	2,425	0	....	92.5	..	28.08	162.80	9.87	1,604				
11/14	1,950	0	....	92.0	46	28.08	162.80	9.87	1,604	4.492	1.211	1.150	+2.130

* The studies in the nitrogen metabolism of the diabetics were made by Dr. C. E. Roser, at that time a member of the medical staff of the University Hospital. His heroic labors at the time of the last influenza epidemic unfortunately resulted in his death. We who knew him realize that medicine has lost one of her most promising devotees. All his work was characterized by zeal, intelligence and rugged honesty. We take this opportunity of acknowledging our deep indebtedness to him in this investigation, and of expressing our grief occasioned by his loss.

† The patient left the hospital at this time without permission and during one day ate about 75 gm. protein, 60 gm. fat, 371 gm. carbohydrate, equal to 2,350 calories. Returned next day.

Atwater and Bryant's Food Tables, and the output in the urine and stool was quantitatively determined by the Kjeldahl method. Eight cases were completely studied in this way. We present, in Table 3, the data obtained from one of these, Case 7 (19-444).

It will be seen from this table that 25 gm. of protein daily were not sufficient to establish nitrogen balance in the short time allowed, whereas 28 gm. were more than enough. Theoretically, on the basis of 0.66 gm. protein per kilogram of body weight, this patient requires 26

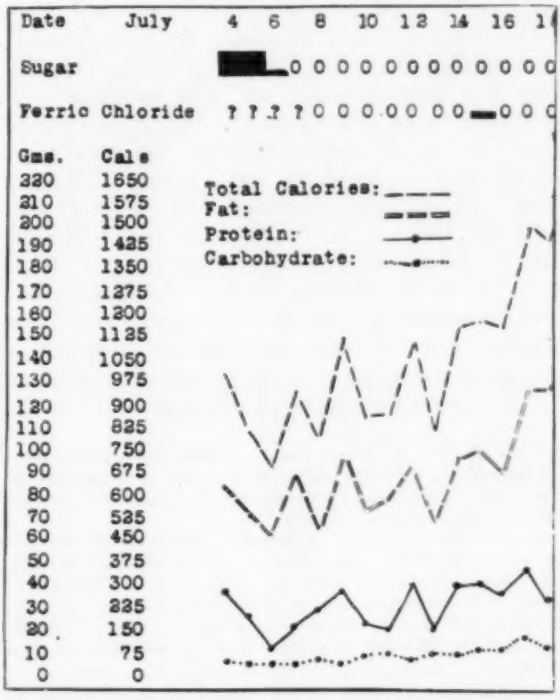

Fig. 3.—Showing absence of acidosis in a child fed a high fat, low protein diet.

gm. protein daily, computed from a weight of eighty-eight pounds. At his discharge weight, he would require 28 gm. of protein daily. But, as already pointed out, it has been shown for normal man that the "two-thirds of a gram per kilo" rule may be expected to supply more than enough nitrogen. This same relationship holds in this diabetic patient, who, when eating 0.66 gm. of protein per kilo of body weight has an excess of more than 2 gm. daily over nitrogen balance.

The other cases studied by this method showed a similar relationship between protein need and body weight, and convinced us that nitrogen balance could be safely maintained by feeding 0.66 gm. of protein per kilogram of body weight in the diabetic as in the normal man. This makes any argument on this score against our high fat, low protein diet, untenable.

A diabetic diet, in order to be satisfactory, must be capable of enabling the patient to lead a moderately active life for an indefinite period. As has already been pointed out, the severe diabetic may be kept sugar free by a sufficient reduction of his total caloric intake, but it is frequently necessary to reduce the total calories so much when protein is used as the chief source of energy that such patients suffer from slow starvation, and are quite incapable of earning a livelihood—indeed many of them may be said to merely exist. From the point of view of the patient, who does not fully appreciate the dangers of continued hyperglycemia, such a situation is a poor exchange for that which he had before treatment. While our experience with the high fat diet has been brief in relation to the chronicity of the disease and we are not in a position to discuss the eventual results of our diet, we are, nevertheless, greatly impressed by the excellent condition of our patients months after leaving the clinic. The strength and capacity for work of some of our younger patients is astonishing to one who has seen many severe diabetics treated by the older methods. We cite a few cases as examples of this point.

Case 8 (No. 20-19).—A young man, 22 years old, entered the clinic Jan. 16, 1920, weighing 113 pounds. After five weeks of treatment he was discharged on a diet containing 2,000 calories, of which 40 gm. were protein, 25 gm. carbohydrate and the remainder fat.

Since then, he has returned at frequent intervals for examination. On every occasion he has been sugar free, and he has gained 9 pounds in weight. May 7, less than four months after he came to us, he began working in a machine shop, at a stamping machine, which keeps him on his feet constantly. August 20 when last seen by us, he stated that he was feeling entirely well, that he had had no difficulty in doing his work and that he found his diet very pleasant.

Case 9 (No. 19-286).—A man, aged 40, who had had glycosuria for ten years before coming to us, entered the clinic because he was continuously losing weight and strength, because of increasing numbness of the feet, accompanied by prickling sensations in the legs, and because of serious and increasing impairment of vision. On admission, June 5, 1919, his blood sugar was 0.4 per cent. By June 9, as a result of our diet containing 900 calories, he was sugar free. By June 25 his diet had been increased to 2,500 calories and consisted of 243 gm. fat, 48 gm. protein, and 15 gm. carbohydrate. He was discharged June 30, 1919, with this diet, weighing 129 pounds.

March 30, 1920, nine months later, he returned for examination stating that he had felt entirely well during the interval and that he had had no difficulty in carrying on his work as a traveling salesman. He weighed 124 pounds and his urine was sugar free.

CASE 10 (No. 20-420).—A woman, aged 32 years, entered the clinic June 5, 1920, complaining of weakness of more than a year's duration. Her condition had become such that she had not been able to do her housework, and if she walked about she fainted. She was started on our routine high fat diet containing 900 calories and became sugar free in five days. Her diet was increased by the usual steps until it reached from 1,800 to 2,000 calories of which about 170 gm. were fat. She left the hospital June 15, 1920, on this diet. A month later she returned for examination stating that she had gained 3 pounds and that she was doing her housework for the first time since January, 1919. Her urine was sugar free and there was no reaction with ferric chlorid.

SUMMARY

Patients with severe diabetes, as a class, do not remain sugar free on the usual high protein diet unless the total energy intake is kept so low that incapacity from starvation results. The only satisfactory diet is one which will keep the diabetic sugar free, which will prevent the occurrence of serious acidosis, which will maintain nitrogen balance and which will make it possible for him to resume the ordinary activities of life. With these four points in mind, we studied the effect of a high fat, low protein, low carbohydrate diet in the treatment of diabetes. Our experience with this type of diet in the management of seventy-three diabetics has convinced us that it is capable of fulfilling these four specifications.

APPENDIX

Following are examples of high fat, low protein, low carbohydrate diets of varying caloric value.

DIABETIC DIET NO. 1. EXAMPLE 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Chicken, 2 oz.	12.2	1.4	....	61.6
with butter, ⅔ oz.	0.2	17.0	....	153.8
Cabbage, 2 oz.	0.9	0.18	3.18	17.8
with vinegar, salt and pepper.				
Asparagus, 3 oz.	1.53	0.18	2.8	18.9
with butter, ⅓ oz.	0.1	8.5	....	76.9
3 olives, medium size	0.12	4.6	1.94	50.0
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Lettuce, 2 oz.	0.68	0.18	1.64	10.8
with mayonnaise, 1⅓ oz. (oil, 1 oz.)	....	28.35	....	255.1
Tomatoes, 4 oz.	1.02	0.18	3.4	19.2
with butter, 10 gm.	0.1	8.5	....	76.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Lettuce, 2 oz.	0.68	0.18	1.64	10.8
with ground bacon, 1 oz.	2.98	18.37	....	177.2
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	20.51	87.62	14.6	929.0

DIABETIC DIET No. 1. EXAMPLE 2

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 1 oz	5.72	6.35	....	80.0
Spinach, 3 oz	1.77	0.27	2.73	20.4
with vinegar, salt and pepper.				
Asparagus, 3 oz	1.29	0.09	2.37	15.3
with butter, 20 gm	0.20	17.0	....	153.8
Tea	....	.....	....	....
Broth	....	.....	....	....
Supper				
Cabbage, 2 oz	0.9	0.18	3.18	17.8
with ground bacon, ⅓ oz	1.49	9.18	....	88.6
String beans, 3 oz	1.95	0.27	6.3	35.4
with French dressing.				
Oil, 1 oz	....	28.35	....	255.1
Vinegar, ⅓ oz., salt and pepper.				
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Bacon, ⅔ oz	2.1	13.96	....	125.0
1 egg	6.03	4.72	....	66.5
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	21.46	80.37	14.58	858.0

DIABETIC DIET No. 1. EXAMPLE 3

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Cottage cheese, 1 oz	5.92	0.28	1.21	31.1
Lettuce, 2 oz	0.68	0.18	1.62	10.8
with mayonnaise, 1 oz	....	20.04	....	191.4
Tomatoes, 3 oz	1.02	0.18	3.39	19.2
with butter, ⅓ oz	0.1	8.5	....	76.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Cabbage, 1⅓ oz	0.67	0.13	2.38	46.6
with mayonnaise, 1⅓ oz. (oil, 1 oz.)	....	28.35	....	255.1
Spinach, 4 oz	2.36	0.36	3.64	27.2
with butter, ⅓ oz	0.14	12.4	....	108.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
1 egg	6.03	4.72	....	66.6
with butter, ⅓ oz	0.1	8.5	....	76.9
Cream, 1⅓ oz. (18%)	1.2	8.4	2.1	88.8
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	18.22	91.68	14.34	999.5

DIABETIC DIET No. 1. EXAMPLE 4

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Steak, 2 oz.	9.31	8.67	....	115.7
with butter, ⅓ oz.	0.1	8.5	....	76.9
Cabbage, 2 oz.	0.9	0.18	3.18	17.8
with ground bacon, 1 oz.	2.98	18.37	....	177.2
Tomatoes, 3 oz.	1.02	0.18	3.49	19.2
Broth	....	.....	....	....
Supper				
Lettuce, 2 oz.	0.60	0.18	1.64	10.8
with mayonnaise, 1⅓ oz.	....	28.35	....	255.2
Asparagus, 3 oz.	1.53	0.18	....	18.9
with butter, ⅔ oz.	0.2	17.0	....	153.8
Tea	....	.....	....	....
Broth	....	.....	....	....
Breakfast				
Lettuce, 2 oz.	0.68	0.18	1.64	10.8
with vinegar, salt and pepper.				
½ hard cooked egg	3.01	2.36	....	33.3
Broth	....	.....	....	....
Coffee	....	.....	....	....
Total	20.41	84.15	12.75	889.6

DIABETIC DIET No. 1. EXAMPLE 5

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 1½ oz. (medium fat)	8.41	8.35	....	113.2
Asparagus salad:				
Lettuce, 1 oz.	0.34	0.09	0.82	5.4
Asparagus, 3 oz.	1.53	0.18	2.8	18.9
Mayonnaise, 1⅓ oz. (oil, 1 oz.)	....	28.35	....	255.2
String beans, 2½ oz.	1.6	0.22	5.2	29.5
with butter, ½ oz.	0.14	12.04	....	108.9
Broth	....	.....	....	....
Tea	....	.....	....	....
Supper				
Tomatoes, 3 oz.	1.02	0.18	3.39	19.2
Lettuce, 1 oz.	0.34	0.09	0.82	5.4
with mayonnaise, ⅔ oz. (oil, ½ oz.)	....	14.2	....	127.6
Broth	....	.....	....	....
Tea	....	.....	....	....
Breakfast				
Omelet: 1 egg	6.03	4.72	....	66.6
Butter, ⅓ oz.	0.1	8.5	....	16.9
Cream, 1 oz. (18%), for coffee	0.8	5.6	1.4	59.2
Broth	....	.....	....	....
Total	20.31	83.02	14.43	886.2

DIABETIC DIET No. 2. EXAMPLE 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Chicken, 2 oz.	12.2	1.42	....	61.6
with butter, 1 oz.	0.28	24.09	....	217.9
Beets, 3 oz.	1.35	0.09	8.25	39.3
with butter, ½ oz.	0.14	12.04	....	108.9
String beans, 3 oz.	1.95	0.27	6.3	35.4
with ground bacon, ½ oz.	1.49	9.18	....	88.6
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Lettuce salad:				
Shredder lettuce, 2 oz.	0.68	0.18	1.64	10.8
Chopped onion, ½ oz.	0.22	0.04	1.4	6.9
Mayonnaise, 2 oz. (oil, 1⅓ oz.)	.....	42.53	....	82.6
Tomato bisque:				
Tomatoes, 1 oz.	0.34	0.06	1.13	6.4
1 bouillon cube	.....	.....	....	.....
Cream, (40%), 2 oz.	1.24	22.68	1.7	215.8
Hot water to fill bowl	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Bacon, 1 oz.	2.98	18.37	....	115.7
Egg, 1	6.03	4.72	....	66.6
Cream (18%), 1 oz., for coffee	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	29.70	141.27	21.82	1,415.7

DIABETIC DIET No. 2. EXAMPLE 2

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Fish, 1⅔ oz.	8.41	4.86	....	52.5
with butter, ½ oz.	0.15	12.75	....	115.4
Cabbage, 2 oz.	0.90	0.18	3.18	17.8
with cream (18%), 1 oz.	0.80	5.60	1.4	59.2
Tomatoes, 3 oz.	1.02	0.18	3.39	19.2
with butter, ½ oz.	0.15	12.75	....	115.4
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Asparagus, 3 oz.	1.29	0.09	....	15.5
with mayonnaise, 2 oz. (oil, 1⅔ oz.)	.....	42.53	....	382.6
Lettuce, ⅔ oz.	0.68	0.17	....	10.8
with bacon, ½ oz.	1.49	9.18	....	86.6
Custard:				
Cream (18%), 2 oz.	1.60	11.2	2.8	118.4
2 egg yolks	2.71	9.98	....	109.0
Tea	.....	.....	....	.....
Broth	.....	.....	....	.....
Breakfast				
1 egg	6.03	4.72	....	66.6
Spinach, 3 oz.	1.77	0.27	2.73	20.4
with butter, ½ oz.	0.15	12.75	....	115.4
Cream (18%), 2 oz., for coffee	1.60	11.2	2.8	118.4
Broth	.....	.....	....	.....
Total	28.75	138.42	20.31	1,423.0

DIABETIC DIET No. 3. EXAMPLE 1

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Trout, 2 oz	10.26	5.84	....	93.6
butter, ½ oz	0.14	12.04	....	108.9
Asparagus salad:				
Lettuce, 1 oz	0.34	0.09	0.82	5.4
Asparagus, 3 oz	1.29	0.09	2.37	15.33
Mayonnaise, 2 oz	.....	42.53	....	382.6
Celery, 3 oz	0.93	0.09	....	15.6
Watermelon, 3 oz	0.33	0.18	5.07	25.8
Tea	.....	.....	....	.....
Broth	.....	.....	....	.....
Supper				
Tomatoes, 4 oz	1.36	1.24	4.52	25.6
with butter, ½ oz	0.14	12.04	....	108.9
Egg salad:				
Shredded lettuce, 2 oz	0.68	1.18	1.84	10.8
1 hard cooked egg	6.03	4.72	....	66.6
Mayonnaise, 2 oz. (oil, 1½ oz.)	.....	42.53	....	382.6
Diabetic jello	1.36	.....	4.1	21.8
with whipped cream, 2 oz	1.24	22.68	1.7	215.8
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Omelet, 1 egg	6.03	4.72	....	66.6
1 egg yolk	2.7	5.0	....	54.5
Butter, ½ oz	0.14	12.4	....	108.9
Cream (18%), 2 oz., for coffee	1.6	11.2	2.8	118.4
Broth	.....	.....	....	.....
Total	34.22	176.21	26.24	1,827.7

DIABETIC DIET No. 3. EXAMPLE 2

Dinner	Gm. Protein,	Gm. Fat,	Gm. Carbohyd.,	Calories
Chicken, 2 oz	12.2	1.42	....	61.6
creamed with egg	6.03	4.72	....	66.6
18% cream, 2 oz	1.6	11.2	2.8	118.4
Beets, 3 oz	1.35	0.09	8.25	39.3
with butter, ½ oz	0.14	12.04	....	109.8
String beans, 3 oz	1.95	0.27	6.2	34.5
with ground bacon, ½ oz	1.49	9.18	....	88.6
Walnuts, ½ oz	2.61	9.13	1.84	100.0
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Cabbage salad:				
Lettuce, ½ oz	0.17	0.04	0.41	2.7
Cabbage, 1½ oz	0.67	0.13	2.38	13.3
Onion, 1½ oz	0.22	0.04	1.4	6.9
Mayonnaise, 2 oz. (oil, 1½ oz.)	.....	42.53	....	382.6
Celery, 1 oz	0.3	0.04	0.92	5.2
Tomato bisque:				
Tomatoes, 2 oz	0.68	0.12	2.26	12.8
Cream (40%), 2 oz	1.24	22.68	1.7	215.8
Hot water to fill bowl.				
Tea	.....	.....	....	.....
Breakfast				
Bacon, 1 oz	2.98	18.37	....	177.2
Lettuce, 2 oz	0.68	0.18	1.64	10.8
with mayonnaise, 2 oz	.....	42.53	....	382.6
Broth	.....	.....	....	.....
Coffee	.....	.....	....	.....
Total	34.31	174.71	29.8	1,826.6

DIABETIC DIET NO. 3. EXAMPLE 3

Dinner	Gm. Protein,	Gm. Fat,	Gm. Carbohyd.,	Calories
Trout, 2 oz.	10.26	5.84	....	46.8
with butter, 1 oz.	0.28	24.09	....	217.9
Green onions, 1 oz.	0.45	0.09	2.8	13.8
Sliced tomatoes, 4 oz.	1.36	0.24	4.52	25.6
with mayonnaise, 2 oz. (oil, 1½ oz.)	.....	42.53	....	382.6
String beans, 3 oz.	1.95	0.27	6.2	35.4
with ground bacon, ½ oz.	1.49	9.18	....	88.6
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Spinach, 3 oz.	1.77	0.27	2.73	20.4
with butter, ½ oz.	0.14	12.04	....	108.9
Cabbage, 2 oz.	0.9	0.18	3.18	17.8
with vinegar, salt and pepper.				
Diabetic custard:				
Cream (18%), 3 oz.	2.4	16.8	4.2	177.6
Egg yolks, 2	4.7	0.9	....	109.0
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Bacon, ⅔ oz.	1.98	12.24	....	118.1
1 egg	6.03	4.72	....	66.6
Butter, 1 oz.	0.28	24.09	....	217.9
Cream (18%), 1 oz.	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	34.78	167.10	25.03	1,706.2

DIABETIC DIET NO. 3. EXAMPLE 4

Dinner	Protein, Gm.	Fat, Gm.	Carbohyd., Gm.	Calories
Boiled ham, 2 oz. (medium fat)	6.93	16.5	....	176.2
Tomato salad:				
Lettuce, 1 oz.	0.34	0.09	0.82	5.4
Tomatoes, 3 oz.	1.02	0.18	3.39	19.2
Mayonnaise, 2 oz. (oil, 1½ oz.)	.....	42.53	....	382.6
Onions, 3 oz.	1.35	0.27	8.4	41.4
with butter, ½ oz.	0.14	12.04	....	108.9
Celery, 1 oz.	0.31	0.03	0.93	5.2
Coffee	.....	.....	....	.....
Tea	.....	.....	....	.....
Supper				
Asparagus, 4 oz.	1.72	0.12	3.16	20.4
with butter, 1 oz.	0.28	24.09	....	217.9
Spinach, 4 oz.	2.86	0.36	3.04	27.2
with bacon, 1 oz.	1.49	9.18	....	88.6
Diabetic junket:				
Milk, 5 oz.	2.82	3.39	4.23	58.8
with whipped cream (1⅓ oz.)	0.83	15.12	1.15	143.8
Broth	.....	.....	....	.....
Tea	.....	.....	....	.....
Breakfast				
Spanish eggs:				
Butter, 1 oz.	0.28	24.09	....	217.9
Chopped onion, ½ oz.	0.22	0.04	1.4	6.9
Tomatoes, 1 oz.	0.34	0.06	1.13	6.4
Eggs, 2	12.06	5.44	....	133.2
Cream (18%), 1 oz., for coffee	0.8	5.6	1.4	59.2
Broth	.....	.....	....	.....
Total	33.29	159.13	29.63	1,719.2

CLINICAL CALORIMETRY

XXIX. THE METABOLISM IN TUBERCULOSIS *

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INTRODUCTION

In regard to the dietary of tuberculous patients medical opinion has fluctuated within wide limits. The extent of this fluctuation may be seen by an examination of the data collected by Fisher,[1] regarding the dietaries given patients by ninety-five of the leading sanatoriums of the world. In this list the total number of calories fed daily ranges from a maximum of 5,500 to a minimum of 2,140. The number of grams of protein varies from 60 to 190 per diem. To the practical physician, who is faced with the problem of selecting the best type of dietary to prescribe for tuberculous patients, the problem is quite bewildering. To make the selection it is necessary to know, first, the total energy transformations in such patients and, second, the extent of destruction of protein by the toxins of the disease and the minimum amount of protein which must be given to maintain the patient in nitrogen equilibrium. A search of the literature for this information yields unsatisfactory results because of the meagerness of the data and of the fact that most of the work was done before the advent of the most accurate methods of study.

HISTORICAL

For a very complete and comprehensive compilation of the work done prior to 1903 one may refer to Ott.[2] A great part of this work, in which it appears that the technic used was crude and experimental conditions poorly controlled, will be omittted in our references. Some of it is of great historical interest, as for instance, the work of Nysten[3] carried out in Paris in 1811. By means of a respiratory valve he separated the inspired from the expired air, which he collected in a bladder during a measured period of time. This air was analyzed

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† During 1916-1917 Dr. Wm. H. Olmstead of St. Louis assisted in the work.

1. Fisher, Irving: Proc. Sixth Internat. Congr. on Tuberculosis **1**:694, Part 2, 1908.

2. Ott, A.: Die chemische Pathologie der Tuberculose, Berlin, 1903.

3. Nysten: Ueber die chemischen Atmungserscheinungen in Krankheiten, Meckel's Deutsch. Arch. f. Physiol. **3**:264, 1817.

for carbon dioxid by shaking it with lime water (over mercury in a graduated cylinder), the oxygen then being absorbed by phosphorus. Calculation of the energy transformation from the gaseous exchange could not be done at that time, but the physiologic principle is the one most commonly used today. This work is most significant when one considers that it was contemporary with the development of percussion of the chest by Auenbrugger, and the invention of the stethoscope by Laennec.

Although the physical diagnosis of the disease progressed by leaps and bounds, the next study of the respiratory exchange was not made until by Hannover,[4] who studied the production of carbon dioxid in five patients with phthisis. The body weight is given and the carbon dioxid per minute. By assuming an average respiratory quotient of 0.80, we may calculate the daily heat production of these patients as between 1,200 and 2,100 calories per day, and from 26.5 to 40 calories per kilogram of body weight. In 1878 Moeller [5] studied three poorly nourished patients with phthisis, males weighing from 44 to 45 kg., aged from 24 to 48 years. The carbon dioxid produced was measured in the Pettenkoffer-Voit apparatus in six hour periods. These patients all had food and beer, so that the metabolism was not basal. Assuming an average respiratory quotient of 0.80, the daily heat production would be between 1,600 and 1,780 calories, or from 35 to 40 calories per kilogram of body weight.

The first work in which the finding of normal respiratory quotients may be taken as evidence of good technic is that of Loewy,[6] who studied exchange of oxygen and carbon dioxid, minute volume respired and nitrogen excretion at different body temperatures after tuberculin injections, using the Zuntz-Geppert appparatus. He found that there was only a moderate increase in oxygen consumption in fever and that it was greater with rising than with falling temperatures. In three of his cases, which were incipient, the minute volume respired increased slightly, but in a fourth case with extensive tuberculosis there was a rather close parallelism between the oxygen consumed and the minute volume. This observation is one of extreme practical importance, as will be seen later.

In the same year Kraus and Chvostek [7] studied five phthisical patients with a Zuntz-Geppert apparatus. In some of the cases the

4. Hanover: De quantitate relativa et absolute acidi carbonici ab homine sano et aegroto exhalati, Copenhagen, 1845, p. 82.

5. Moeller: Kohlensäureausscheidung der Menschen bei verkleinerter Lungenoberfläche, Ztschr. f. Biol. **14**:542, 1878.

6. Loewy, A.: Stoffwechseluntersuchungen im Fieber und bei Lungenaffectionen, Virchow's Arch. f. path. Anat. **126**:218, 1891.

7. Kraus and Chvostek: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Tuberculininjection, Wien. klin. Wchnschr. **4**:104, 127, 1891.

respiratory quotients lie beyond the limits of possibility. These are the first investigators to give the height of the patient so that the surface area may be calculated. The conditions were not basal, as the patient was not fasting. However, calculations show that an increase of 39 per cent. in the metabolism increased the minute volume respired from 7,743 c.c. to 10,000 c.c., in a case in which proper quotients were obtained.

Work done by Speck [8] may be mentioned also, since it shows in many cases a marked parallelism between the amount of carbon dioxid produced and the minute volume. The respiratory quotients are either so low or so high as to make the results of doubtful value. Data relative to the amount of food taken and muscular activity are not given. Robin and Binet [9] give mass statistics regarding the minute volume, lung capacity, oxygen consumption and respiratory quotients of 162 phthisical patients. Averages only are given, the methods used are not stated, and there has been no attempt to compare individual patients with normals of the same size, so that the data are not very satisfactory. However, it is of interest to note that the minute volumes respired were from 80 to 110 per cent. greater than those of the normals studied. They also found a consumption of oxygen from 70 to 100 per cent. greater. The respiratory quotients were lower in the tuberculous patients. Lung capacity was also greatly reduced.

Staehelin [10] studied a tuberculous patient during a night sweat in a Jacquet respiration chamber. Food was taken before the observation and the subject was very restless. He concluded, however, that the metabolism was not raised and that sweating had no influence on the total metabolism.

In a recent study of the effect of acetyl salicylic acid on the heat regulation in fever Barbour [11] used three tuberculous subjects. These subjects were studied in a Benedict respiration chamber under basal conditions. The basal metabolism in these three cases was only from 3 to 4 per cent. above the average normal.

The absorption of food in tuberculosis has been studied by Blumenfeld,[12] who found that the percentage losses of nitrogen and fat in the stools were within normal limits. However, in certain cases there was marked interference with absorption. Biedert [13] reported a case

8. Speck: Physiologie des menschlichen Athmens, 1892.
9. Robin and Binet: Bull. méd. Par. **15**:249, 1901.
10. Staehelin, R.: Der respiratorische Gaswechsel eines Phthisikers während des Nachtschweisses, Ztschr. f. klin. Med. **66**:241, 1908.
11. Barbour, Henry G.: Arch. Int. Med. **24**:624 (Dec.) 1919.
12. Blumenfeld, F.: Ueber die diaetetische Verwerthung der Fette bei Lungentuberculose, Ztschr. f. klin. Med. **28**:417, 1895.
13. Biedert: Die Tuberculose des Darms und des lymphatischen Apparats, Jahr. f. Kinderh. **21**:172, 1884.

TABLE I.—Alcohol Checks for 1916-17

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat			Oxygen			Carbon Dioxid			Water			R. Q. Theory 0.667
			Theory, Cal.	Found, Cal.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	
5/17/16 92.92	1	13.49	87.63	87.20	−0.5	25.80	26.35	+2.1	23.65	23.34	−1.3	15.47	16.09	+4.0	0.644
	2	13.26	87.23	87.41	+0.2	25.69	24.75	−3.7	23.55	23.34	−0.9	15.40	15.91	+3.3	0.686
	3	13.72	90.26	89.24	−1.1	26.58	26.29	−1.1	24.36	23.90	−1.9	15.93	16.26	+2.1	0.661
Average	...	.....	88.37	87.94	−0.5	26.02	25.80	−0.8	23.85	23.59	−1.1	15.60	16.09	+3.1	0.665
10/3/16 92.92	1	12.05	79.27	82.02	+0.9	23.34	23.31	−0.1	21.40	21.42	+0.1	13.99	15.14	+8.2	0.668
	2	12.78	84.07	86.45	+2.8	24.76	25.05	+1.2	22.69	22.57	−0.5	14.84	15.76	+6.2	0.655
Average	...	.....	81.67	84.24	+3.1	24.05	24.18	+0.5	22.05	22.00	−0.2	14.42	15.45	+7.2	0.662
10/10/16 92.92	1	12.83	84.41	83.51	−1.1	24.85	24.93	+0.3	22.78	22.42	−1.6	14.90	15.27	+2.5	0.654
	2	13.16	86.57	87.06	+0.6	25.49	24.94	−2.2	23.37	23.42	+0.2	15.28	15.79	+3.3	0.683
	3	13.36	87.89	85.42	−2.8	25.88	25.88	0.0	23.72	23.39	−1.4	15.51	15.76	+1.6	0.657
Average	...	.....	86.29	85.34	−1.1	25.41	25.25	−0.6	23.29	23.08	−0.9	15.23	15.61	+2.5	0.665
12/4/16 92.92	1	11.97	78.75	80.57	+2.3	23.19	22.63	−2.4	21.25	20.92	−1.6	*33.90	31.40	−7.4	0.672
	2	11.68	76.84	77.80	+1.2	22.63	22.37	−1.4	20.74	20.78	+0.2	33.57	30.89	−8.0	0.676
	3	11.33	74.54	76.88	+3.1	21.95	21.21	−3.4	20.12	19.67	−2.2	33.16	30.63	−7.6	0.674
Average	...	.....	76.71	78.42	+2.2	22.59	22.07	−2.3	20.70	20.46	−1.2	33.54	30.97	−7.2	0.674
2/28/17 92.44	1	11.94	78.14	78.15	0.0	23.01	22.66	−1.5	21.09	20.61	−2.3	13.85	14.39	+3.9	0.662
	2	11.91	77.96	78.32	+0.5	22.95	22.18	−3.4	21.04	21.09	+0.2	13.83	13.62	−1.5	0.691
	3	12.12	79.32	80.64	+1.7	23.36	23.13	−1.0	21.41	21.19	−1.0	14.06	14.37	+2.2	0.666
Average	...	.....	78.47	79.04	+0.7	23.11	22.66	−2.0	21.18	20.96	−1.0	13.91	14.13	+1.6	0.673
4/23/17 92.44	1	12.62	82.59	82.93	+0.4	24.32	23.01	−5.4	22.29	21.47	+3.7	14.64	14.58	−0.4	0.678
	2	11.39	74.54	75.36	+1.1	21.95			20.12			13.22	13.83		
	3	13.40	87.70	87.98	+0.3	25.82	46.92	−1.8	23.67	42.92	−2.0	15.55	15.45	+1.8	0.665
Average	...	.....	81.61	82.09	+0.6	24.03	23.31	−3.0	22.03	21.46	−2.6	14.47	14.62	+0.6	0.669
Totals.....	.....	.....	1397.70	1406.96	+0.7	411.57	405.61	−1.4	377.25	372.45	−1.3	307.10	305.14	−0.6	0.668

* 20 gm. extra water introduced.

of fat diarrhea in a child with tuberculosis of the intestine, mesenteric lymph nodes and peritoneum. Also Friederich Mueller [14] found a loss of 32.9 per cent. of fat and 7.9 per cent. of nitrogen in the stools of a patient with tuberculous ulcers in the intestine and marked amyloidosis which involved the liver very slightly and the pancreas not at all.

The question of the toxic destruction of protein has received much attention. An excellent compilation of this work, with abundant quotations of experimental data, may be found in Ott.[2] The general results of this work tend to show that in the afebrile condition many phthisical patients will readily make large gains in nitrogen. With febrile patients, either with spontaneous fever or with fever following tuberculin injections, small losses of nitrogen occur on diets furnishing about 2,500 calories and from 100 to 150 gm. of protein per diem. These small nitrogen losses would become important only because of the long duration of the disease. The determination of the protein minimum in tuberculosis does not seem to have been made, although it has been the subject of some speculation.

The discussion of the nitrogen losses in phthisis would be incomplete without mention of loss in the sputum. Lanz [15] estimated the daily nitrogen loss in the sputum of sixteen patients with phthisis. The protein loss was calculated from the total nitrogen of the sputum and varied from 1.69 to 7.00 gm. of protein per diem.

METHODS OF STUDY

The respiration calorimeter of the Russell Sage Institute of Pathology was employed. This apparatus has been previously described in Paper 2 of this series.[16] The technic has been essentially that described in Paper 4 of the series,[17] with the few exceptions noted below. Patients were studied 14 to 16 hours after the last regular meal, though each received the small standard breakfast described in Paper 26 of this series.[18] The only effect of this meal was found to be an increase in the metabolism of 2 per cent. in the third hour

14. Mueller, Fr.: Untersuchungen über Icterus, Ztschr. f. klin. Med. **12**:86, 1887.

15. Lanz: Deutsch. Arch. f. klin. Med. **56**:619, 1896.

16. Riche, J. A., and Soderstrom, G. F.: The Respiration Calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital, Arch. Int. Med. **15**:805 (June) 1915.

17. Gephart, F. C., and Du Bois, E. F.: The Determination of the Basal Metabolism of Normal Men and the Effect of Food, Arch. Int. Med. **15**:835 (June) 1915.

18. Soderstrom, G. F., Barr, D. P., and Du Bois, E. F.: The Effect of a Small Breakfast on the Heat Production, Arch. Int. Med. **21**:613-620 (May) 1918.

TABLE 2.—Alcohol Checks for 1919-20

Date and Per Cent. of Alcohol by Weight	Hour	Alcohol Burned, Gm.	Heat			Oxygen			Carbon Dioxid			Water			R. Q. Theory 0.667
			Theory, Cal.	Found, Cal.	Error, per Cent.	Theory, Gm.	Found-Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	Theory, Gm.	Found, Gm.	Error, per Cent.	
12/5/19	1	12.87	81.45	81.16	−0.3	23.99	23.85	−0.1	21.99	21.62	−1.7	14.86	15.18	+2.2	0.659
89.4	2	12.53	79.30	81.48	+2.7	23.35	23.31	0.0	21.40	21.40	0.0	14.47	14.96	+3.4	0.668
	3	12.62	79.91	79.83	0.0	23.53	22.93	−2.6	21.57	21.23	−1.6	14.58	14.92	+2.3	0.673
	4	12.64	80.00	77.78	−2.8	23.56	23.02	−2.3	21.59	20.77	−0.4	14.60	14.90	+2.1	0.657
Average	...	.....	80.17	80.06	−0.1	23.61	23.28	−1.4	21.64	21.20	−1.3	14.63	14.99	+2.5	0.664
2/26/20	1	11.15	70.54	71.91	+1.9	20.77	19.96	−3.9	19.04	18.54	−2.6	12.87	13.22	+2.7	0.675
89.4	2	10.84	68.56	68.14	−0.6	20.19	21.39	+5.9	18.51	17.74	−4.2	12.52	12.73	+1.7	0.603
	3	11.21	70.95	71.75	+1.3	20.89	20.45	−2.1	19.15	18.65	−2.9	12.95	13.28	+2.5	0.663
Average	...	.....	70.02	70.60	+0.8	20.62	20.60	−0.1	18.90	18.31	−3.1	12.78	13.08	+2.3	0.646
2/28/20	1	10.98	69.47	69.11	−0.5	20.45	20.30	−0.7	18.75	18.08	−3.5	12.68	13.58	+7.1	0.648
89.4	2	10.67	67.52	68.38	+1.3	19.88	20.14	+1.3	18.22	17.21	−5.5	12.32	13.32	+8.1	0.621
	3	10.31	65.23	66.57	+2.1	19.21	19.02	−1.0	17.61	16.47	−6.5	11.90	12.94	+8.7	0.630
Average	...	.....	67.41	68.02	+0.9	19.85	19.82	−0.2	18.19	17.25	−5.2	12.30	13.28	+8.0	0.633
3/15/20	1	11.66	73.81	74.30	+0.7	21.73	19.22	−11.5	19.92	19.67	−1.3	13.47	14.07	+4.5	0.745
89.4	2	11.31	71.56	71.29	−0.4	21.07	20.44	−3.0	19.31	18.92	−2.0	13.06	13.30	+1.8	0.673
	3	11.15	70.56	71.90	+1.9	20.78	21.03	+1.2	19.04	18.74	−1.6	12.88	13.63	+5.8	0.648
	4	11.19	70.80	71.13	+0.5	20.84	20.80	−0.2	19.11	18.54	−3.0	12.92	13.34	+3.3	0.648
Average	...	.....	71.08	72.16	+0.7	21.11	20.37	−3.5	19.35	18.97	−2.0	13.08	13.59	+4.0	0.677
3/18/20	1	11.70	72.96	75.22	+3.1	21.48	21.25	−1.1	19.69	19.47	−1.1	13.49	13.84	+2.6	0.666
3/22/20	1	12.64	78.80	82.09	+4.9	23.20	22.35	−3.7	21.27	20.85	−2.0	14.57	15.11	+3.7	0.678
88.1	2	12.22	76.22	80.18	+5.2	22.44	22.20	−1.1	20.57	20.34	−1.1	14.09	14.60	+3.6	0.666
	3	12.27	76.51	79.60	+4.0	22.53	22.19	−1.5	20.65	20.09	−2.7	14.15	14.66	+3.6	0.659
Average	...	.....	77.18	80.82	+4.7	22.72	22.25	−2.1	20.83	20.43	−1.9	14.27	14.79	+3.6	0.668
5/6/20	1	12.27	76.53	77.41	+1.2	22.53	22.24	−1.3	20.66	20.11	−2.7	14.15	14.64	+3.5	0.658
88.1	2	11.89	74.15	74.88	+1.0	21.83	21.21	−2.8	20.01	19.49	−2.6	13.71	14.29	+4.2	0.668
	3	11.88	74.09	75.64	+2.1	21.82	21.76	−0.3	20.00	19.67	−1.7	13.70	14.29	+4.3	0.658
Average	...	.....	73.92	75.98	+2.8	22.06	21.73	−1.5	20.22	19.76	−2.3	13.85	14.41	+4.0	0.661
Totals.....	.....	.....	1548.94	1570.35	+1.4	456.07	449.06	−1.5	418.06	407.60	−2.5	283.94	298.80	+5.2	0.660

after eating. As a rule the observations were started in the latter part of the third hour or early in the fourth hour.

In the direct calorimetric calculation of the heat lost from or stored in the body, the rectal temperature was used, taking the specific heat only of the body at 0.83. This figure has been found to give fairly accurate results in a considerable series of normal subjects. At best, however, it can be considered as merely an average figure. For different individuals it must vary considerably, depending on the proportions of the various tissues in the body, especially of fat (specific heat = 0.45) and water (specific heat = 1).[19] Moreover, even though the specific heat is not known exactly, it may be considered to remain constant during short periods. The body weight for short periods is likewise a constant. With this in view, a comparison in each hour of the heat production (calculated from the respiratory exchange) with the heat elimination (measured directly) will show that the change in the rectal temperature does not always parallel that of the average body temperature.

The surface area in each case was determined from the height and weight by the "height-weight chart" of Du Bois and Du Bois.[20] In calculating the variations of the metabolism from the average normal, based upon the surface area, the normal heat production per square meter of body surface has been taken from the table given by Aub and Du Bois,[21] which takes into account the effect of age. If the predictions of the normal metabolism for each individual in the series based upon the figures of Aub and Du Bois are compared with the predictions for the same individuals made from Benedict's tables[22] the average difference between the two predictions will be found to be about 3 per cent.

ALCOHOL CHECKS

Interspersed throughout the series were a number of alcohol checks. The first four cases of the series were studied in 1917. The alcohol checks for that period are to be found in Table 1. As the calorimeter had not been in use during the war it was necessary to make quite a number of checks before the apparatus was finally put in good condition. A satisfactory check was first obtained on Dec. 5, 1919, so

19. Rubner, M.: Kalorimetrie, Tigerstedt's Handb. d. physiologische Methoden, Hirzel, Leipzig, 1911, **1**:170, Part. 3.

20. Du Bois, Delafield, and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**:863 (June) 1916.

21. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

22. Harris, J. A., and Benedict, F. G.: A Biometric Study of the Basal Metabolism in Man, Carnegie Int. Wash., 1919, Pub. 279.

that patients were not studied until after that date. The results of the alcohol checks for 1919-1920 are given in Table 2.

During all of the previous work with the calorimeter a special soda lime was used.[23] This same soda lime was used up to Feb. 12, 1920. At this time a new soda lime, which had been devised for use in submarines, was introduced. This product contained relatively little sodium hydroxid and, consequently, the water formed in the reaction with carbon dioxid was not held in the soda lime but passed off rapidly into the sulphuric acid of the last absorber in the train. The efficiency of this latter absorber was not great enough to handle all of this moisture. The result is seen in examining the alcohol checks for February 26 and 28, and March 15. In these checks the carbon dioxid found was too low, while the results for oxygen consumed and for heat check fairly well. The effect of this error is to give respiratory quotients which are too low. The results for the direct calorimetry are quite satisfactory, and the error in the indirect calorimetry is small, since the indirect calculation is based on the oxygen, for which better checks were obtained.

After March 15, 1920, the Stanley Jordan soda lime was again used, the checks for March 18 and 22 being satisfactory for the purpose of this study.

REPORT OF CASES[24]

CASE 1.—Charles G. *Tuberculosis of pleurae and peritoneum.*

History.—A laborer, 31 years of age, born in the United States, was admitted to the service of Dr. Charles Nammack in Bellevue Hospital April 13, 1917, and discharged unimproved June 3, 1917.

September, 1916, he had pleurisy with effusion on the left side. March 12, 1917, he began to feel pain, localized to a small area in the epigastrium. He had much flatulence. Five days later he noticed that his abdomen was swollen. He had been constipated and the pain had steadily increased in intensity. He had severe night sweats but no cough.

Physical Examination.—Patient was a poorly developed, emaciated negro; height 165 cm.; weight 52.4 kg. The tongue showed a white coat. There were signs of fluid on the right side of the chest to one inch below the spine of the scapula and, on the left, to the angle of the scapula. There was harsh breathing, with many râles above the level of the fluid. The heart was overacting. The rate was rapid, 120 or more, when the patient was in dorsal decubitus. The abdomen was tense and offered a boggy resistance to palpation. There was dulness in both flanks and a distinct fluid wave.

Laboratory Examination.—Urine showed a trace of albumin, hyaline and granular casts. The sputum was examined but no tubercle bacilli were found. Usually his cough was unproductive. The roentgenogram showed pleural effusion on both sides, but no lung involvement.

April 14, in the general ward, the abdomen was tapped and 3,800 c.c. of cloudy, blood-tinged fluid were removed. A guinea-pig, injected with this

23. Made by the Stanley Jordan Company, New York.

24. The first four cases were studied by D. P. Barr in 1917; the remainder by W. S. McCann in 1919-1920.

fluid, died of intercurrent infection April 30, showing no sign of tuberculosis. April 23 the right chest was tapped and 1,500 c.c. of cloudy, straw-colored fluid were removed.

May 7 he was admitted to the metabolism ward. He was observed in the calorimeter May 8, 11 and 14. With temperature varying from 37.8 to 38.1 C., his basal metabolism was 13 per cent. above the average normal. His right chest was tapped a second time May 15 and 400 c.c. of thick, bloody fluid were withdrawn. While in the ward he ran a remittent temperature. The symptoms remained unchanged. He maintained his weight and had an excellent appetite. June 3 he was discharged unimproved.

TABLE 3.—Diet Chart and Nitrogen Balance in Case 1

Name and Date	Food			Food N, Gm.	Urine N, Gm.	Feces N, Gm. (Estimated)	Excreta N, Gm.	N Balance, Gm.	Body Weight, Kg.
	Total Calories	Carbohydrate, Cals.	Fat, Cals.						
Charles G.									
5/ 8/17	2,247	925	981	13.3	12.5	1.3	13.8	−0.5	53.1
5/ 9/17	2,233	967	880	14.7	11.2	1.5	12.7	+2.0	
5/10/17	2,179	908	909	14.1	11.2	1.4	12.6	+1.5	52.5
5/11/17	2,225	860	1,006	14.0	12.5	1.4	13.9	+0.1	
5/12/17	2,668	1,017	1,257	15.4	13.4	1.5	14.9	+0.5	
5/13/17	2,733	1,110	1,229	15.4	13.5	1.5	15.0	+0.4	53.5
5/14/17	1,575	636	686	10.0	9.0	1.0	10.0	0.0	
5/15/17	2,639	1,159	1,082	15.5	13.6	1.6	15.2	+0.3	53.7
5/16/17	2,614	1,057	1,166	15.3	11.9	1.5	13.4	+1.9	
5/17/17	1,580	899	595	3.4	8.3	1.0	9.3	−5.9	53.0
5/18/17	2,637	1,383	1,167	3.4	8.3	1.0	9.3	−5.9	53.2
5/19/17	2,635	1,280	1,268	3.4	4.9	1.0	5.9	−2.5	53.7
5/20/17	2,575	1,269	1,221	3.3	4.5	1.0	5.5	−2.2	52.4
5/21/17	2,548	1,261	1,211	3.0	5.0	1.0	6.0	−3.0	52.7
5/22/17	2,400	1,061	1,255	3.3	5.1	1.0	6.1	−2.8	52.8
5/23/17	2,091	947	1,072	2.8	4.3	1.0	5.3	−2.5	52.2
5/24/17	2,635	1,114	1,136	15.0	8.2	1.5	9.7	+5.3	52.5
5/25/17	2,875	1,482	1,300	3.6	5.9	1.0	6.9	−3.3	52.6
5/26/17	2,973	1,705	1,189	3.1	5.2	1.0	6.2	−3.1	52.6
5/27/17	2,961	1,690	1,185	3.0	4.4	1.0	5.4	−2.4	52.7
5/28/17	2,735	1,421	1,224	3.1	4.8	1.0	5.8	−2.7	52.9
5/29/17	3,167	1,950	1,142	2.9	4.7	1.0	5.7	−2.8	52.1
5/30/17	3,138	1,886	1,178	2.9	4.7	1.0	5.7	−2.8	52.4
5/31/17	3,019	1,828	1,108	3.4	5.0	1.0	6.0	−2.6	52.1
6/ 1/17	2,905	1,570	1,260	2.9	4.9	1.0	5.9	−3.0	

Case 2.—Trellis H. *Tuberculosis of lungs and lymph nodes.*

History.—A waiter, 24 years of age, born in the United States, was admitted to the service of Dr. Robert J. Carlisle May 3, 1917, and discharged unimproved May 22, 1917. The history was not satisfactory because of the very limited intelligence of the patient. In 1913 he had empyema, for which he was treated at the Presbyterian Hospital in Chicago.

April 15 he noticed for the first time a mass beneath the chin on the left side, which grew rapidly. About two weeks later he found that a similar, smaller mass had appeared on the right side. He had had an occasional dry, tickling cough, but no night sweats.

Physical Examination.—Patient was a poorly developed, poorly nourished boy, mentally deficient, height 168 cm., weight 51.6 kg. The teeth showed a marked pyorrhea and were in very bad condition. In the submental region and at the angles of the jaw there were large, hard, semi-elastic, painless masses. The swelling at the angle of the jaw on the right side was hot and showed slight fluctuation. There was a chain of very hard, discrete glands in the right groin; another of similar character in the left axilla.

Lungs: At both apices anteriorly and posteriorly there was dulness to percussion. There was high pitched, almost tubular breathing over the left apex posteriorly and there were a few subcrepitant râles over the right apex.

Laboratory Examination.—The urine was negative. Blood: Leukocytes, 8,200; polymorphonuclears, 69 per cent.; erythrocytes, 4,400,000; hemoglobin, 75 per cent. Wassermann negative. Von Pirquet positive. The roentgenogram showed marked peribronchial infiltration in the left upper lobe between the first and third ribs. The sputum was repeatedly examined, but no tubercle bacilli were found.

May 9: Basal metabolism, with temperature from 40.1 to 40.2 C., was 29 per cent. above the average normal, and with temperature between 39.7 and 40.1 C., it was 43 per cent. above the average normal, due, in part, to coughing.

His condition did not change while in the hospital. His temperature was irregular. May 22 he was transferred to a tuberculosis sanitarium.

Case 3.—Robert W. *Pleurisy with effusion.*

History.—A ship's carpenter, 39 years of age. He was admitted April 23, 1917, and discharged improved on June 2, 1917. He had been in the Navy for eight years. For the past six years he had been on mercantile vessels. In 1900 he had pneumonia, with which he was ill for one month. He had always been a very heavy drinker. He denied venereal disease.

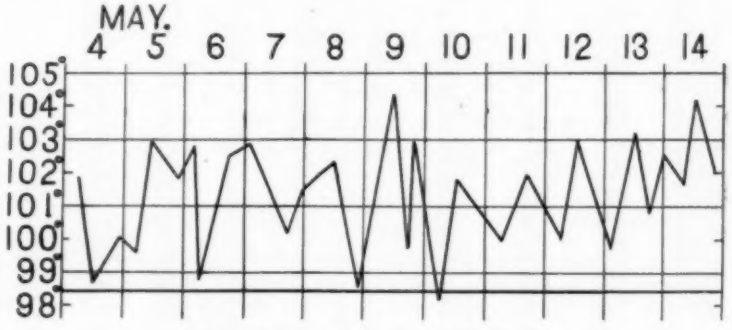

Fig. 1.—Temperature chart of Trellis H.

April 13 he began to feel short of breath, coughed frequently and had some pain in the epigastrium and along the sternum. Coughing or deep breathing increased the pain.

Physical Examination.—Patient was a well developed, rather emaciated man who showed a moderate degree of cyanosis, height 165 cm.; weight 53.4 kg. Lungs: There was absence of fremitus, flatness on percussion, distant voice and distant bronchovesicular breathing over the entire left lung. The right lung was normal. Heart: Was pushed to the right. The right border was 8 cm. to the right of the midsternal line. The left border of dulness merged with flatness of fluid. Coughing was unproductive.

Physical Examination.—One sample of sputum was obtained, but contained no tubercle bacilli. Urine: negative. Blood: Leukocytes, 8,400; polymorphonuclears, 64 per cent.; lymphocytes, 27 per cent. Roentgenogram showed pleurisy with effusion on the left side, but indicated no lung involvement.

April 24, 1,400 c.c. of straw-colored fluid were removed from the left chest. No tubercle bacilli were found. April 26, after 2,000 c.c. had been withdrawn, there were still signs of fluid. May 3 the chest was again filled with fluid, 3,500 c.c. of which were withdrawn. May 15 the level of the fluid was from the middle of the scapula behind to the third rib in front. May 17 1,400 c.c. were withdrawn, after which the level of fluid was at the eighth rib in the midscapular line. May 25 at 8:15 a. m. he had a chill, the cause of which was

not apparent. On the same day, from 10:30 a. m. to 2:30 p. m., he was observed in the calorimeter, temperature falling from 40.10 to 39.36 C., metabolism 29 per cent. above the average normal.

He was in the calorimeter May 28 while the temperature was normal. In the course of this observation, however, he was seized with abdominal pain. During the rest of the day he had a diarrhea, and passed fourteen stools which contained much blood and mucus. This continued until May 31. Careful examination of the centrifugalized stools revealed no tubercle bacilli. June 2 he was discharged from the hospital. His temperature was normal. The signs of fluid did not change after May 17.

CASE 4.—George P. *Acute miliary tuberculosis; tuberculoma of left eye.*

History.—A laborer, 18 years of age, born in Greece, was admitted April 23, 1917, and discharged June 12, 1917. He came to this country from Greece in January, 1917. He had never had any serious illness.

The latter part of March, 1917, he lost his appetite, felt feverish, and had several night sweats. A few days later he found that he could not see with his left eye. He had coughed continually since the onset of the trouble, and for a month had sharp, stabbing pain in the left side of the chest. Since he came to this country he had lost twenty-five pounds in weight, dropping from 154 to 129 pounds.

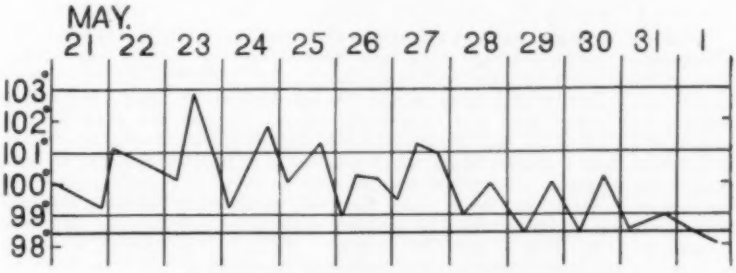

Fig. 2.—Temperature chart of Robert W.

Physical Examination.—Patient was a well developed, moderately emaciated boy, height 172 cm., weight 58.5 kg. His face showed a high color and his vasomotor system was very unstable. The eyes were normal externally. The retina of the right eye was normal. In the left retina there was a tumor, white in color, above and to the temporal side of the optic disk, about two disks in width, three disks in length. It was elevated six diopters above the surrounding retina. There was a small hemorrhage into the retina on the temporal side of the tumor. Lungs: There was a dulness to percussion and prolonged, high pitched, bronchial breathing at the right apex posteriorly. Anteriorly there were many constant, fine râles. At the left base there were many coarse, leathery friction râles. The cervical, axillary and inguinal lymph nodes were palpable.

On later examination, April 22, the tumor in the left retina was found to be elevated eleven diopters and to have spread to involve the optic disk.

Laboratory Examination.—Urine: negative. Blood: Leukocytes, 7,000; polymorphonuclears, 70 per cent.; erythrocytes, 3,600,000. Tuberculosis fixation test was positive. Questionable tubercle bacilli were found once in the sputum. The roentgenogram showed a diffuse miliary tuberculosis with a cavity at the right apex.

May 24, he was observed in the calorimeter; temperature varied from 37.5 to 37.8 C.; basal metabolism, 11 per cent. above the average normal.

The cough and pain in the chest continued and were very troublesome. With the exception of the rapid growth of the tuberculoma in the left eye, his condition changed very little after admission to the hospital. He was sent to a tuberculosis sanitarium June 12.

TABLE 4.—Diet Chart and Nitrogen Balance in Case 4

Name and Date	Total Food, Cals.	Carbohydrate, Gm.	Fat, Gm.	Food N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Weight, Kg.
George P.							
5/24/17	1,800	208	72	10.6	10.0	+0.8	58.6
5/25/17	2,500	241	120	15.1	11.8	+3.3	58.6
5/26/17	2,530	230	125	15.6	13.4	+2.2	58.1
5/27/17	2,530	242	122	15.8	17.4	−1.6	58.5
5/28/17	2,580	283	110	15.0	15.1	−0.1	58.4
5/29/17	2,930	430	122	2.9	10.2	−7.3	
5/30/17	3,140	458	127	3.0	6.4	−3.4	59.2
5/31/17	3,040	449	119	3.5	5.5	−2.0	
6/ 1/17	2,960	395	136	3.1	5.1	−2.0	
6/ 2/17	2,380	283	123	2.9	4.2	−1.3	58.1
6/ 3/17	2,600	336	123	3.1	5.0	−1.9	
6/ 4/17	2,700	346	128	3.4	4.8	−1.4	58.1

* Fecal nitrogen estimated.

Case 5.—Spencer C. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—A negro, aged 46 years, was admitted Dec. 8, 1919, complaining of shortness of breath, weakness and cough. One brother had died of tuberculosis. The patient's early life had been spent under poor conditions, but his health had been good up to 1916 when he was discharged from the army. Since then his occupation had been that of janitor. During the last two years he had continually "felt below par," progressively losing weight and strength. During this time he had a chronic cough which was worse at night and frequently kept him from sleeping. The cough became productive of a tenacious, greenish sputum in which he had never noted the presence of blood. During the year before admission, the wasting progressed rapidly, so that he was sixty-five pounds below his best weight (163 pounds). He had occasional night sweats. In the past few months he had noted increasing shortness of breath, at first only on exertion, but later while lying in bed. His cough had become so severe as to induce vomiting. One month before admission he had dull pains all over the chest, but these had disappeared. His appetite was whimsical. Bowels were constipated.

Physical Examination.—Patient was a fairly well developed, emaciated negro, lying flat in bed but showing considerable dyspnea, height 169 cm., weight 44.4 kg. Lips showed some cyanosis. Facies showed exhaustion and lethargy. Eyes were very prominent, with considerable bulging of the periocular tissues. The few remaining teeth were carious. The tonsils were markedly enlarged and cryptic. On both sides of the neck there were numerous, enlarged lymph nodes about the size of a bean. Thorax: showed retractions above and below both clavicles. The expansion was poor, but more limited on the right side. Lungs: showed impaired resonance over the entire chest, more marked on the right side. On auscultation bronchial breathing was heard over both upper lobes, with many medium and coarse râles heard over the entire chest. Near the inner end of the spine of the right scapula posttussive suction was heard. Heart: not enlarged. The first sound was of poor quality, the pulmonary second sound was accentuated. Rhythm was regular, but the rate was very rapid. Arteries: thickened but not tortuous.

Blood Pressure: Systolic, 115 mm.; diastolic, 65 mm. Abdominal findings: negative. Lymph nodes: enlarged in neck, axillae, inguinal and epitrochlear regions. Genitalia: normal. Fingers and toes: showed marked clubbing. There was slight edema of the ankles. Reflexes: Achilles and patellar reflexes not obtained.

Laboratory Examination.—The sputum showed numerous tubercle bacilli. Urine: normal, except for low specific gravity. Roentgenogram of chest showed diffuse peribronchial infiltration of the entire right lung, with numerous small cavity formations at the right apex. Numerous foci of peribronchial infiltration scattered irregularly throughout the central portion of the left lung. The temperature course is shown in Figure 3.

The patient was observed in the calorimeter December 10, the basal metabolism being 12 per cent. above the average normal for his surface area during a period of normal temperature.

Patient left hospital two days later and subsequent history is unknown.

Case 6.—Edith B. *Pulmonary tuberculosis, both lungs, with cavitation.*

History.—Colored female, aged 20 years, admitted Dec. 12, 1919, complaining of pain in the left side of chest, cough and weakness. One aunt died of

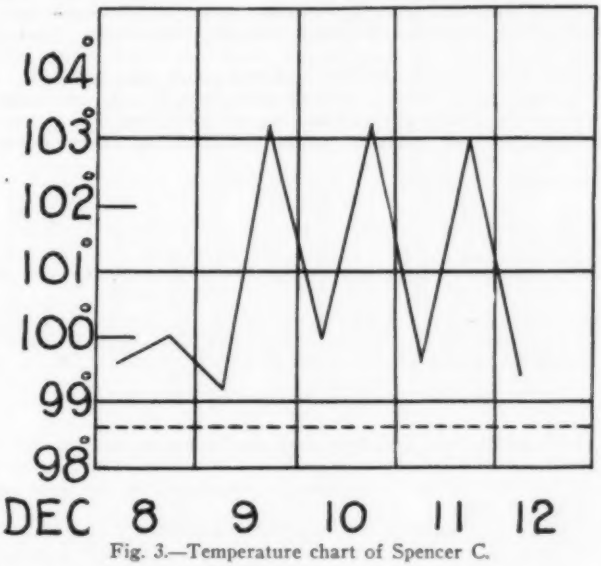

Fig. 3.—Temperature chart of Spencer C.

tuberculosis. Her mother had a disease of the spine with partial paralysis of one leg. The patient had been married eighteen months but had had no pregnancies. In childhood she had whooping cough and measles. In 1916 she had pneumonia. Otherwise her health had been good up to the onset of the present illness. Her normal weight was 135 pounds.

Early in September, 1919, patient became very weak and dizzy about 4 p. m., and at this time she felt chilly. Soon after this she developed a troublesome cough which was much worse at night. She expectorated a moderate amount of mucoid sputum in which no blood was noticed. At this time she was engaged in nursing an aunt who died one month later of consumption. A little later she began to have a great deal of pain in the left side of the chest on coughing and on deep breathing. These symptoms continued to grow worse until she was confined to bed most of the day. Her appetite was very poor. She lost weight, from 135 to 109 pounds. She had "hot fevers" at night, followed by sweats. She was admitted to the service of Dr. James Alexander Miller, through whose kindness she was transferred for study.

Physical Examination.—The patient was a young negro woman, 178 cm. tall, weighing 44.6 kg., alert and intelligent, lying on her side in bed, breathing rapidly and coughing occasionally. Mucous membranes were pale and not cyanotic. Thorax: well formed, but with moderate retractions above and below clavicles, most marked on the left side, involving the second and third interspaces. The expansion of the right side of the chest was fairly free, but there was marked limitation of motion of the left side. Lungs: Percussion note was resonant at both bases, but there was no excursion at the left, while at the right base there was an excursion of 5 cm. Both apices were dull both front and back, more marked on the left. There was diminution of the voice and breath sounds at the left base behind, and over the dull areas the breathing was bronchovesicular or bronchial in character, with many fine râles. Heart: Apex impulse could not be located. The cardiac dulness extended 12 cm. to the left in the fifth intercostal space, but the right border could not be sharply located. Rate rapid; rhythm regular. No murmurs heard. Pulse: rapid and of low tension. Arteries: normal. Abdomen: negative. Genitalia: not examined. Extremities: normal. Reflexes: normal. Epitrochlear lymph nodes: enlarged.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine: normal. Roentgenogram of chest showed infiltration, fibrosis and cavitation of the middle portion of the right lung and the entire left lung with the exception of a small portion of the left base. Cavity formation was located in the upper

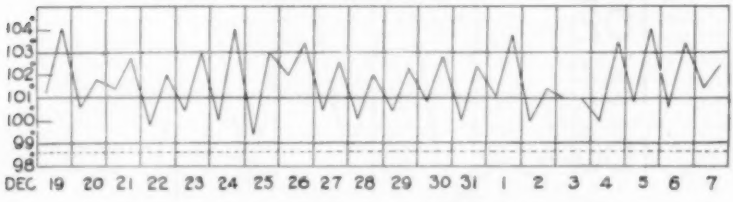

Fig. 4.—Temperature chart of Edith B.

portion of the middle lobe, but there were also numerous small cavities in the left lung. There were many pleuropericardial adhesions, with marked distortion of the cardiac outline. Compensatory emphysema in the right lung and fibrosis in the left lung.

Observations were made in the calorimeter December 7 and 19 and January 6. The first observation made at normal temperature showed no elevation of the basal metabolism. Subsequent observations during high fever, with coughing, raised the metabolism from 18 to 20 per cent. above the average normal and still further increases were due to restlessness during the third observation. The mechanism of temperature regulation in this case is shown graphically in Figure 14.

Case 7.—Harry G. *Pulmonary tuberculosis, extensive bilateral infiltration.*

History.—A fountain-pen maker, 18 years of age, was admitted Jan. 2, 1920. complaining of cough, weakness and night sweats. He had measles in childhood, but was well and active, though rather weak as a boy. At the age of 16 he went to work in a fountain-pen factory, where the work was confining and the atmosphere full of dust. His appetite was poor, bowels constipated, but he had no respiratory symptoms until November, 1919.

At that time he caught cold and began to have a racking cough with a moderate amount of viscid sputum. The cough reached its maximum intensity one month before admission, after which it was less troublesome. It was most severe at night, when it sometimes produced vomiting. He had night sweats

before entering the hospital, but none during his stay. Two weeks before admission he coughed up about one teaspoonful of bright blood. He had become very constipated. He had no urinary symptoms. His greatest weight was 123 pounds; admission weight was 109 pounds. He felt loss of strength very much.

Physical Examination.—Patient was a pale, poorly developed, poorly nourished boy of 18 years, height 163 cm., weight 42.7 kg. There were small but distinctly palpable nodes on both sides of the neck. Thorax was carinate. There was retraction above and below both clavicles, more marked on the left side. The entire left chest showed retraction and marked limitation of expansion. Lungs: Both upper lobes were dull on percussion, the left to the second intercostal space in front and to the angle of the scapula behind; the right was dull only above the clavicle in front and to the spine of the scapula behind. Over these dull areas the breath sounds were bronchial in quality, with many medium sized and fine râles. No excursion of the left base was found, while the maximum excursion of the right base was 2 cm. At the left base there was slight dulness, bronchovesicular breath sounds and many moist râles, front and back. Heart not enlarged nor displaced. There were no murmurs. The rate was quite rapid, but the rhythm was regular. Pulse was rapid and soft. Blood pressure: Systolic 120 mm.; diastolic 80 mm.

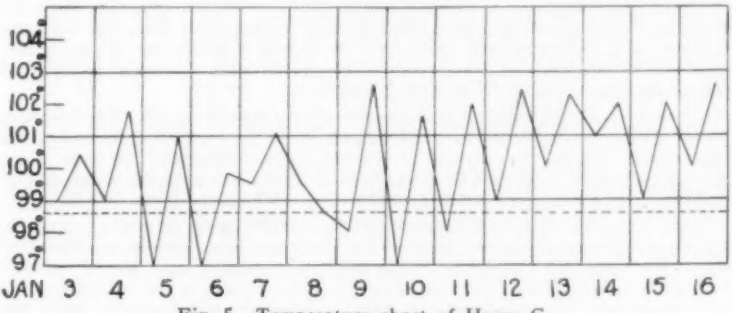

Fig. 5.—Temperature chart of Harry G.

Further examination negative. Urine was normal. Sputum showed numerous tubercle bacilli. Fluoroscopy showed a very diffuse parenchymatous infiltration of both upper lobes, particularly of the left side, with a small antrum beneath the left pole (Dr. J. A. Miller).

One observation was made in the calorimeter January 13. The temperature fell from 39.20 to 38.94 C., pulse 120. The metabolism was 21 per cent. above the average normal, but the conditions were not basal on account of restlessness.

CASE 8.—Joseph D. *Pulmonary tuberculosis, infiltration of both upper lobes and left base.*

History.—A machinist, aged 33 years, was admitted Dec. 3, 1919, complaining of pain in the left side of the chest and cough. His father, mother and one brother died of pneumonia and one uncle died of "lung trouble." In childhood he had dysentery, mumps, whooping cough, "chills and fever." In 1915 he was treated for "lung trouble" in a hospital. He had a bad cough at that time. While under treatment he worked for one year. In April, 1919, he was in Bellevue Hospital on account of pleurisy and cough. Following this he had a chronic cough and occasionally night sweats. He was very short of breath on exertion and had palpitation but no edema. His appetite was good, bowels regular. He urinated three to four times during the night. He had gonorrhea fifteen years ago. His best weight was 135 pounds.

Nov. 25, 1919, while digging a trench, he felt a sudden, sharp pain in the left side of the chest and across the back. He stopped work but did not go to bed. Pain and cough increased daily so that he entered the hospital December 3. At that time the physical findings, confirmed by the roentgen ray, led to a diagnosis of bilateral apical tuberculosis. The temperature range was from 97.4 to 100 F. Leukocytes, 14,000, with polymorphonulcears 65 per cent.; lymphocytes, 23 per cent.; large mononuclears, 10 per cent.; eosinophils, 1 per cent. Hemoglobin, 73 per cent. Urine was normal.

He was allowed to leave the hospital on pass, but did not return. He was readmitted Jan. 14, 1920, with a temperature of 102 F., having had severe chills.

Physical Examination.—A well developed, fairly well nourished man, height 177 cm., weight 59 kg., face flushed, eyes bright, respirations rapid but not labored. Chest: Retraction of both supraclavicular and infraclavicular fossae. Expansion limited most markedly on the right side. Lungs: Both apices were dull from the second intercostal space in front to the spine of the scapula behind and there was dulness at the left base behind. Breath sounds at both apices were tubular, with crepitant and moist râles. In the left chest in front there was a coarse friction rub between the fourth and seventh intercostal spaces. At the left base behind many coarse râles were heard. Heart was not enlarged; rate 80; rhythm regular; no murmurs. Pulse was full and soft, artery not thickened. Further examination was negative.

The patient improved rapidly though he had a moderate, irregular fever for about nine days. January 15 he complained of huskiness of the voice and pain in the larynx on swallowing. Examination showed a thickening of the arytenoids and of the anterior commissure. The cords were thickened and lacked the normal luster but approximated throughout.

Laboratory Examination.—Sputum showed no tubercle bacilli. The roentgen ray showed a patch of peribronchial infiltration in the peripheral portion of the right apex. There was fibrosis of the left apex, emphysema of both lungs, more on the right. There was production of fibrous tissue in the lower lobe of the left lung, but no peribronchial infiltration. Adhesions at the left base.

Diagnosis.—Early second stage tuberculosis, right apex; fibroid tuberculosis, left apex; interstitial inflammation of the left lower lobe; pleural thickening of the right upper lobe; deviation of the heart to the right, axis almost vertical.

The last day of fever was January 16. He was put in the calorimeter on the seventeenth, at which time his basal metabolism was found to be 90 per cent. of the average normal in one hour in which he was very quiet.

CASE 9.—Michael C. *Pulmonary tuberculosis with cavitation, laryngeal tuberculosis.*

History.—A furrier, aged 33 years, complained of hoarseness and shortness of breath. He was in perfect health up to January, 1919, when he engaged in a drinking bout with some friends. He sang very loudly and on the following day he was quite hoarse. Soon a cough developed with some expectoration. No medicine gave any relief, his cough and hoarseness grew worse, he began to have night sweats and to lose weight and strength. He remained at work, however, until August, 1919. At this time he became very short of breath and felt great oppression of the chest. His cough was more and more productive, but hemoptysis occurred on only one occasion and then in very small amount. He spent November and December in Colorado, where he improved somewhat. Two weeks before admission he returned to New York. He caught cold and had a recurrence of his worst symptoms. He developed complete aphonia. His best weight was 130 pounds; admission weight was 110 pounds.

Physical Examination.—Fairly well developed but emaciated man, height 179 cm., weight 50 kg., lying flat in bed, breathing rapidly, extremely weak and ill. Laryngeal examination was difficult, but showed marked congestion of epiglottis, arytenoids and vocal cords and laryngeal walls. There were a few enlarged lymph nodes in the neck on both sides. Thorax was well formed,

but there were retractions above and below both clavicles. Expansion was limited on both sides, but more so on the right. Lungs: Both apices dull to percussion, right front dull to the fifth rib and behind to the angle of the scapula. The left apex was dull from the second rib to the middle of the scapula behind. Over the dull areas the breathing was in general broncho-vesicular, with many fine and medium moist râles. Over the third intercostal space in the mid-clavicular line the breathing was amphoric in character. Further examination was negative.

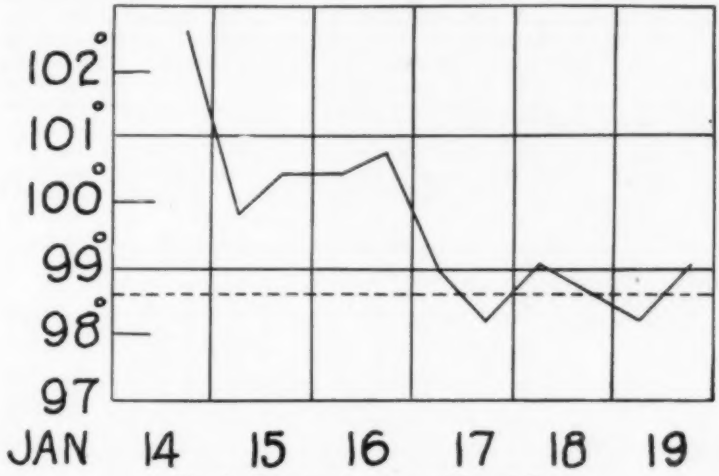

Fig. 6.—Temperature chart of Joseph D.

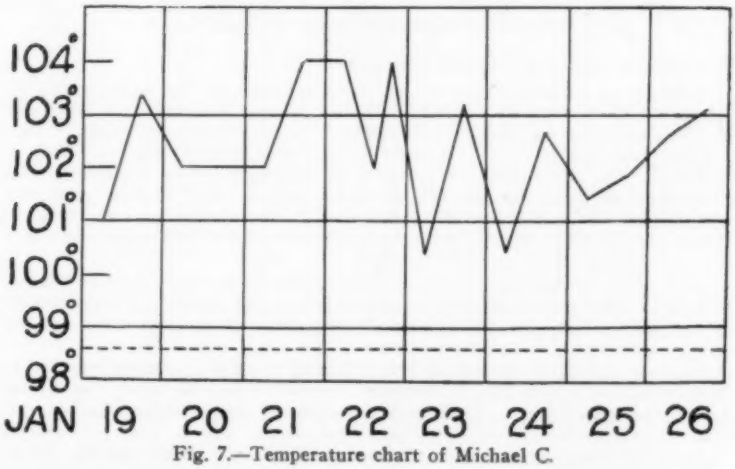

Fig. 7.—Temperature chart of Michael C.

Pulse ranged from 86 to 128 and respirations from 22 to 28. Sputum was full of tubercle bacilli. Urine was normal.

The patient was observed in the calorimeter Jan. 22, 1920. With the rectal temperature falling from 39.8 to 39.2 C. and pulse 120, the metabolism was 31 per cent. the first hour and 24 per cent. the second hour above the average normal; the conditions were not basal as the patient coughed incessantly. The subsequent history is unknown.

Case 10.—Anna H. *Bronchopneumonia; phthisis.*

History.—Sewing machine girl, aged 17 years, was admitted Jan. 25, 1920, complaining of pain in the chest and cough. She had worked two years in the factory, during which time her weight had dropped from 122 pounds to 113 pounds. She was well up to the onset of the present illness, which began Nov. 25, 1919, with a bad cold. The cold did not improve, but she remained at work until Jan. 11, 1920, when her illness became acute, with severe cough and pains in the chest. After remaining in bed for two days she attempted to return to work. She became worse rapidly, coughed constantly and had night sweats. Her weight dropped from 113 to 90 pounds.

Physical Examination.—On admission, January 25, the pharynx was congested, tongue coated, heart normal. Lungs showed no dulness, but numerous, squeaking râles were heard on both sides in back. Temperature, 103 F.; pulse, 100.

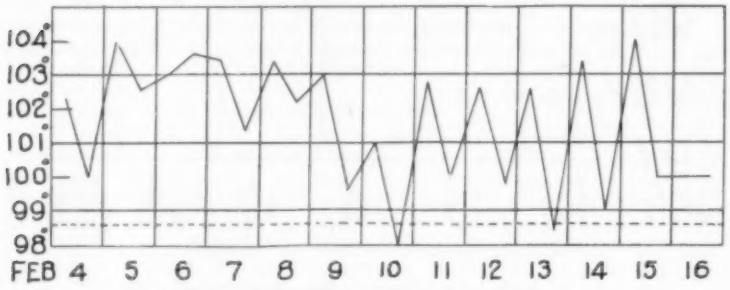

Fig. 8.—Temperature chart of Anna H.

Tentative Diagnosis.—Acute bronchitis.

January 28 numerous tubercle bacilli were found in the sputum. On the following day a note was made: "Thorax symmetrical and well developed. Respiratory excursion is slightly restricted. There are no retractions or bony prominences. There is a widespread process extending through all lobes of both lungs, but most advanced at the bases, characterized by bronchovesicular breathing, and many fine, medium and large moist râles. At both bases posteriorly there is dulness, most marked at the left. At the apex of the heart there is a localized systolic murmur. Over the base of the heart there is a longer, rough murmur heard in systole."

Laboratory Examination.—Urine examinations were all normal. Blood: Feb. 4: Leukocytes, 10,000; polymorphonuclears, 70 per cent.; transitionals, 2 per cent.; lymphocytes, 25 per cent.; eosinophils, 3 per cent. Hemoglobin, 60 per cent.

She was studied in the calorimeter February 5. The temperature rose from 39.38 to 39.64 C.; pulse 132. The metabolism was 21 per cent. above the average normal, but was not basal, as the patient was coughing throughout the observation.

February 7 the physical examination was as follows: "A normally developed girl of 17, past puberty, very emaciated and pale, height 165 cm., weight 41 kg. There is a bright flush over the left malar region; eyes are bright; breathing very rapid but not labored. Thorax shows limitation of expansion of the left

side. There are retractions above the clavicles, and on the left side in the first and second interspaces and at the left base and axilla. Lungs are dull at both apices, and the left lung is dull throughout. The right base is resonant below the angle of the scapula. Over the dull area there is an increase in vocal and tactile fremitus, tubular breathing at the apices and bronchovesicular breathing at the left base. Over the whole chest fine, medium and coarse moist râles are heard. Heart is normal. Pulse rapid, 120, regular, and of very low tension. Abdomen is somewhat distended, but otherwise normal." Further examination was negative.

February 20 the signs of consolidation were intensified. Numerous crackling râles and in many places creaking friction rubs were heard.

The patient died two days later. A necropsy was not permitted.

CASE 11.—John H. *Pulmonary tuberculosis.*

History.—A chauffeur, aged 25 years, was admitted complaining of pain in the chest, headache and chills. He was well and strong up to the time of his enlistment in the British Army, Tank Service, in 1916. He served nine months at the front and remained well until he was gassed with chlorin. He was sick for three or four months with cough and afternoon fever, but was finally returned to duty. He remained well and was discharged physically fit. He was able to do all sorts of work up to the end of November, 1919, when he

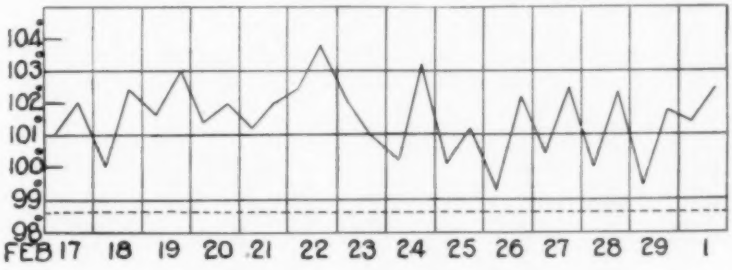

Fig. 9.—Temperature chart of John H.

was taken sick with pneumonia and treated in the Metropolitan Hospital for four weeks. He had been out of the hospital only three weeks when he was again taken sick and admitted to Bellevue Jan. 24, 1920. Three days before admission patient had a severe cough and soreness in the chest. He went to bed and stayed there until the following day. A doctor gave him some whisky. He took it and the next day was admitted in an intoxicated condition. Later he said his best weight was 142 pounds and that he had maintained this up to November. Present weight, 100 pounds.

Physical Examination.—Height, 175 cm., weight 45 kg. Well developed, pale, emaciated young man. Lips somewhat cyanotic and parched. Chest: Well formed with deep supraclavicular fossae. Expansion was fairly good, but more limited on the right side. Lungs: Left apex was dull from the second rib in front to midscapula behind, with bronchovesicular breathing and many fine râles. Left base was resonant except in midaxilla, where there was slight dulness and a creaking rub was heard. The right lung was dull throughout, most marked at the apex, where the breath sounds were tubular and accompanied by fine râles. At the right base the breathing was bronchovesicular, with many medium and fine râles. Heart was normal in size and position; no murmurs. Rhythm was regular. Pulse was soft and rapid. Blood pressure: Systolic 100; diastolic 60. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte counts, January 26, 10,500; February 6, 13,600; polymorphonuclears, 64 per cent.; transitionals, 18 per cent.; lymphocytes, 4 per cent.; large mononuclears, 13 per cent.; eosinophils, 1 per cent. Roentgenogram of chest, February 9, showed diminished illumination over the upper halves of both pulmonic fields. There was considerable increase in the size, number and density of the pulmonic markings throughout this area. These markings were confluent. There was considerable increase in density of both hilus shadows. The costophrenic sinuses were clear. The diaphragmatic outlines were normal. The heart shadow was slightly displaced to the left. Infiltration of upper halves of both lungs.

Diagnosis.—Tuberculosis.

He was studied in the calorimeter February 10. With a normal temperature his basal metabolism was 15 per cent. above the average normal. February 12, the specific dynamic effect of a meat meal was studied (Fig. 15). This meal

TABLE 5.—DIET CHART AND NITROGEN BALANCE IN CASE 11

Name and Date	Food			Food N, Gm.	Urine N, Gm.	Feces N, Gm.	Excreta N, Gm.	N Balance, Gm.	Body Weight, Kg.
	Total Calories	Carbohydrate, Gm.	Fat, Gm.						
John H.									
4/17/20	1,650	147	88	10.7	9.0	1.1	10.1	+0.6	44.6
4/18/20	1,977	185	92	14.2	....	1.4			
4/19/20	1,800	194	78	13.8	9.0	1.4	11.4	+2.4	44.3
4/20/20	.....	...	...	....	6.8	...	....	.....	44.7
4/21/20	.....	...	...	....	10.8				
4/23/20	1,800	156	95	14.5	....	1.5	....	.....	43.8
4/27/20	1,848	152	93	14.1	14.5	1.4	15.9	—1.8	
4/28/20	1,848	152	93	14.1	17.6	1.4	19.0	—4.9	44.0
4/29/20	1,848	152	93	14.1	13.7	1.4	15.1	—1.0	44.2
4/30/20	1,904	173	95	14.4	12.3	1.4	13.7	—0.7	43.9
5/ 1/20	1,904	173	95	14.4	11.6	1.4	13.0	+1.4	43.8
5/ 2/20	2,055	180	100	15.0	11.6	1.5	13.1	+1.9	
5/ 3/20	2,123	185	104	15.7	13.9	1.6	15.5	+0.2	44.3
5/ 4/20	1,734	169	92	7.1	7.6	2.1*	9.8	—2.6	
5/ 5/20	1,739	169	93	7.1	8.8	2.1*	10.9	—3.8	44.7
5/ 6/20	1,739	169	93	7.1	5.7	2.1*	7.8	—0.7	44.7
5/ 7/20	1,737	169	92	7.1	6.4	2.1*	8.5	—1.4	
5/ 8/20	1,737	169	92	7.1	3.8	2.1*	6.9	+0.2	44.7
5/ 9/20	1,737	169	92	7.1	5.6	2.1*	7.7	—0.6	
5/10/20	1,737	169	92	7.1	5.4	2.1*	7.5	—0.4	44.9
5/11/20	2,075	186	121	3.2	5.4	1.0	6.4	—3.2	44.8
5/12/20	2,055	185	121	3.3	4.6	1.0	5.6	—2.3	44.5
5/13/20	1,914	181	118	3.0	3.7	1.0	4.7	—1.7	44.0
5/14/20	1,914	181	118	3.0	3.1	1.0	4.1	—1.1	44.3
5/15/20	1,915	181	118	3.0	....	...	....	.....	44.2

* Analysis made. Remaining fecal nitrogen estimated.

consisted of 350 gm. of lean beef and 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 69.3 calories per hour, his metabolism rose in successive hours after the meal to 77.0, 82.4 and 86.8 calories per hour, respectively. This corresponds closely with the results obtained with normal subjects.

Considerable improvement in the patient's condition occurred, his appetite was better. He still had considerable pain in the left chest.

March 1 his metabolism was 17 per cent. above the average normal, temperature betwen 38.68 and 38.71 C., very quiet.

During the month of March marked improvement continued. The temperature range gradually became smaller and lower. His cough almost ceased. His appetite was good and during this time he was given the ordinary soft, special diet of the hospital, not measured. The total caloric value of this diet is not high. He remained at the same weight, 100 pounds, with very slight variations.

His basal metabolism was again determined April 14; rectal temperature from 37.8 to 37.4 C. His metabolism was 5 per cent. above the average normal. From this his daily basal heat production was estimated at 1,512 calories. This was done as a preliminary to complete dietary control in the metabolism ward. The temperature and graphic record of this study are given in Figure 18. The observed data are given in Table 5. The stools for the different periods were marked off with carmine and saved for analysis, the total nitrogen for the period was determined, and the daily average added to the urine nitrogen figure. The study was made to determine the minimum level at which nitrogen balance could be attained and the minimum to which the protein metabolism could be reduced as a means of estimating the toxic destruction of protein.

CASE 12.—William H. *Pulmonary tuberculosis, tuberculosis of hip joint.*

History.—A laborer, aged 31 years, was admitted in February, 1920, complaining of pain in the chest, cough, loss of weight and weakness. At the age of 2 he had whooping cough and later measles. When 3 years old he had hip disease, for which he was treated at the Postgraduate Hospital. He wore a brace until the age of 13. During this period his health was good. His growth was normal. He had always done hard manual labor outdoors until shortly before the present illness. Late in the fall of 1919 he worked in a factory

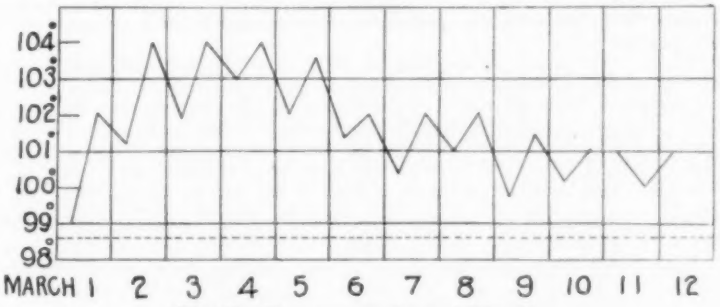

Fig. 10.—Temperature chart of Wm. H.

where he was confined in a dusty room. He felt wretched during his stay in this position and gave it up. He then worked on the city streets shoveling snow. February 7 he became very wet and was exposed all day. He felt a sudden, sharp pain in the left chest and back. In the Bellevue Dispensary tubercle bacilli were found in the sputum and, therefore, he was admitted to the hospital. During the week prior to admission he had night sweats, severe cough, with abundant sputum in which no blood was noted. His best weight was 135 pounds, but just before the onset of illness it was 130 pounds. Weight while in the hospital was 110 pounds.

Physical Examination.—Height 165 cm., weight 49.7 kg. Patient was a fairly well nourished young man of medium size who looked acutely ill. Thorax: Slight asymmetry due to a scoliosis. Respiratory movements fairly free and symmetrical. There were no retractions. Lungs: Apices were dull on both sides above and just below the clavicles. Behind, the dulness, which was most marked at the extreme apex, shaded into normal resonance about the level of the sixth dorsal spine. Over the apices the breath sounds were bronchovesicular, with many fine râles. Between the scapula many coarse moist râles and sibilants were heard. Elsewhere the breath sounds were normal. Heart: Of normal size and position. No adventitious sounds were heard. The rate was rapid, rhythm regular. Pulse rapid and soft. Blood pressure: Systolic, 105 mm.; diastolic, 85 mm. There was ankylosis of the left hip, with

complete limitation of motion. The muscles of the left thigh and calf were atrophied. The left leg was two inches shorter than the right. There were no other abnormalities.

Laboratory Examination.—Sputum contained many tubercle bacilli. Urine examinations were normal throughout. Blood: Leukocyte count, March 3, 10,400; hemoglobin, 90 per cent. March 8: Wassermann reaction negative. Roentgen-ray report showed pulmonic fields of equal size. There was diminution of illumination over the upper half of the left pulmonic field. The apices were clear. There was considerable increase in the hilum shadows, with calcific foci on the right. The pulmonic markings were increased in size, number and density over the upper half of the left pulmonic field, with agglutination. Over the right pulmonic field there was increase in the size, number and density of the pulmonic markings, with confluence. There was an irregularity in the outline of the right diaphragm. The costophrenic sinuses were clear. The heart was large, generally rounded in outline and median in position.

March 24: Vital capacity equaled 2,795 c.c. The normal for the present surface area, according to the calculations of West, is $1.53 \times 2{,}500 = 3{,}825$ c.c., but the normal surface area for health is 1.66 square meters, hence the normal vital capacity would be 4,150 c.c.

March 2 the metabolism was 18 per cent. above the average normal when his temperature was 38.58 C. and the patient was very quiet. At the same temperature in the next hour the heat production was raised 5 per cent. more by coughing.

March 10 the basal metabolism was 9 per cent. above the average normal when the rectal temperature was 38.0 C.

The specific dynamic action of a protein meal was studied. The meal consisted of 350 gm. meat with 10 gm. butter (protein 70 gm., fat 28 gm.). From a basal heat production of 65.6 calories per hour, the metabolism rose after the meal to 68.7, 73.9 and 86.1 calories per hour in successive hours. This corresponds closely with the behavior of the normals studied (Fig. 15).

CASE 13.—John S. *Pulmonary tuberculosis, mitral stenosis, and regurgitation, compensated.*

History.—A machinist, aged 28 years, was admitted complaining of a feeling of fatigue and of swelling of the feet and ankles. He had no illness in childhood except occasional sore throat. At the age of 20 he had mumps. In 1913 he had typhoid fever. In 1919 he had two attacks of acute rheumatic fever. He had gonorrhea three times. He was in quite good health until the spring of 1919, when he had a severe cold, which persisted. He had a dry, hacking cough, which grew much worse in the course of several weeks. He lost appetite and began to have fever in the afternoon, with great weakness and prostration. He remained at work even when his temperature was high. Sputum examination by the board of health showed tubercle bacilli. At this time his afternoon temperature was 103 F. His weight dropped from 160 to 154 pounds. He was sent to a hospital for tuberculosis and later transferred to Otisville. He improved, became afebrile, and regained weight up to 160 pounds. While there he developed acute rheumatic fever after lying on the wet grass when overheated from work. He soon recovered, but had another attack in August, 1919. Following the second attack he had edema of the ankles while at work. For the past year he had to urinate three or four times during each night. Maximum weight in 1913 was 168 pounds; weight before illness in 1919 was 160 pounds; weight while in hospital, 148 pounds.

Feb. 5, 1920, his feet began to swell and he felt very tired. This continued, causing him to stop work February 10. He was admitted to Bellevue February 12, with a fever of 104 F., falling to normal in the course of forty-eight hours, and then fluctuating between 99 and 100 F. He had a mild cardiac decompensation from which he rapidly recovered, though he continued to have fever from a reactivation of his tuberculosis.

Physical Examination.—Patient was a well developed man, 191 cm. in height, weighing 62.3 kg. Thorax well formed, supraclavicular fossae deep, but

with greater retraction on the left. There was limitation of expansion of the left chest. Lungs were dull on percussion of both upper lobes, the left upper from the fourth rib in front to the angle of the scapula behind, the right from the third rib in front to the midscapula. Expiration was prolonged and high pitched, with many medium and fine râles. Heart: Apex impulse in the fifth intercostal space was 12 cm. to the left of midline. Dulness extended to the left 13 cm. in the fifth space and to the right 6 cm. in the fourth intercostal space. There was a suggestion of a thrill over the precordium. There was a presystolic murmur of rough, crescendo quality at the apex, and also a systolic murmur heard at the apex, in the axilla and to the right of the sternum in the fourth space. The second pulmonic sound was accentuated. The rate was

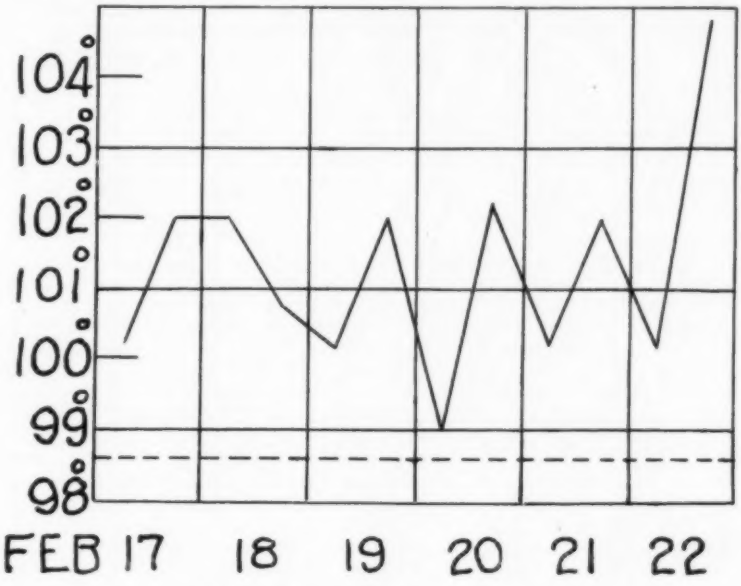

Fig. 11.—Temperature chart of John S.

120, rhythm regular. Pulse was dicrotic. Blood pressure: Systolic, 105 mm.; diastolic, 60 mm. Liver was not felt. Further examination was negative.

Laboratory Examination.—Sputum contained many tubercle bacilli. Blood: Leukocyte count on admission was 14,200, of which 84 per cent. were polymorphonuclears, 4.5 per cent. large mononuclears, 1.5 per cent. transitionals, 9.5 per cent. lymphocytes. Red cell count was 4,152,000. Hemoglobin, 75 per cent. Urine examination was negative.

He was studied in the calorimeter February 17, at which time his basal metabolism was found to be 14 per cent. above the average normal, with temperature falling between 37.8 and 37.4 C. On a second occasion the observation was unsuccessful because he was eliminating water from the skin and lungs at the rate of about 72 gm. per hour, which surpassed the capacity for ventilation of the calorimeter.

Case 14.—George M. *Pulmonary tuberculosis, with cavitation.*

History.—A machinist's helper, aged 31 years, was admitted March 15, 1920, complaining of chills, fever and night sweats and severe cough. In childhood he had whooping cough and measles at the age of 9 years. He was in perfect health until he went to India in 1917 in the transport service of the Mesopotamia campaign. While there he had "sand fly fever," for which he was treated with quinin. He also had dysentery which became chronic. Each winter following 1914 he had colds and persistent cough, nevertheless remaining in fairly good health. His appetite was habitually poor. He had a soft chancre in 1911 and later had gonorrhea also. He has had no secondary manifestations of syphilis. His maximum weight was 137 pounds.

In the winter of 1919-1920 the patient had his usual winter cough, but it was much more severe than usual. It kept him awake at night. He became very weak and "run down." Sputum was never bloody. About February 15 he began to feel chilly in the afternoon and at night he had severe sweats.

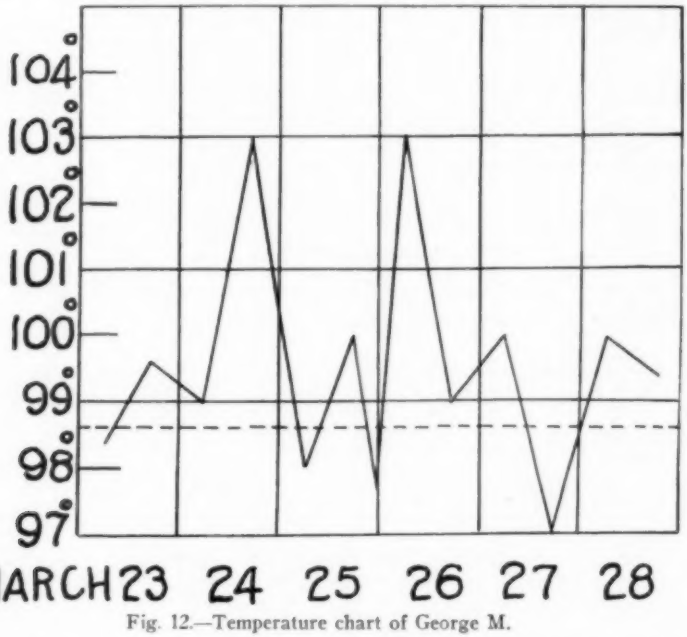

Fig. 12.—Temperature chart of George M.

His cough became worse and the expectoration blood tinged. He had had much substernal and precordial pain, aggravated by coughing. Vomiting was sometimes induced by the severity of the cough.

Physical Examination.—The patient was a small, thin man, 165 cm. tall, weighing 49.1 kg. Thorax of normal shape, but with marked supraclavicular retractions. Respiratory excursions were symmetrical and apparently not limited. Lungs: Both apices quite dull on percussion from the third rib in front to the angles of the scapulae behind. Over the dull areas there was increased fremitus and whispered voice transmission, bronchial breathing and many fine râles. At the right apex the breathing approached amphoric in quality, especially at the extreme upper part of the right axilla. The bases were slightly dull posteriorly and the excursion of neither base exceeded one finger's breadth.

There was bronchovesicular breathing at the right base and a few coarse râles were heard at both bases. Heart not enlarged nor displaced; rate 100; rhythm regular. Blood pressure: Systolic, 85 mm. There were a few palpable nodes in both inguinal regions. Moderate clubbing of fingers. Further findings were negative.

Laboratory Examination.—Sputum examination showed many tubercle bacilli. Urine normal. Blood: Leukocyte count (March 17), 11,400, of which 60 per cent. were polymorphonuclears, 29 per cent. lymphocytes, 9 per cent. large mononuclears, 1 per cent. transitionals, 1 per cent. eosinophils. March 26: Leukocytes, 11,000; polymorphonuclears, 73 per cent.; lymphocytes, 17 per cent.; large mononuclears, 10 per cent.

Vital capacity, average six trials, 2,523 c.c., which is 61 per cent. of the normal, as calculated by the method of West from the surface area.

This patient was observed in the calorimeter March 24 while the temperature was falling rapidly from 39.56 to 38.72 C., with sweating. The metabolism in the first hour was 34 per cent. above the average normal and during the second it was 27 per cent. above. March 26 another observation was made while the temperature fell from 39.23 to 38.17 C., the metabolism being 29 per cent. above the average normal. The percentage of heat lost through vaporization was from 32 to 35 per cent. of the total heat eliminated. This latter observation is graphically represented in Figure 14. The conditions were not basal in either case, due to restlessness.

CASE 15.—Joseph R. *Pulmonary tuberculosis with cavitation; chronic nephritis with hypertension.*

History.—A printer, aged 36 years, was admitted May 3, 1920, complaining of "kidney trouble." While his health, in general, had always been good, he had had for a long time a slight, hacking cough, not productive, believed to be due to excessive smoking. He had been a heavy beer drinker. For many years he had urinated once during the night. His maximum weight was 180 pounds. In 1918 he lost weight rapidly to 161 pounds. His weight remained at 160 until six weeks before admission, when he again began to lose. Weight while in hospital was 134 pounds. About one week before admission he noticed swelling of the ankles and legs, extending within the next few days to the trunk and face. He felt nauseated and had some attacks of vomiting. He then began to urinate five or six times a night. He had not been conscious of fever and had had no night sweats. His cough had become productive, but there had been no hemoptysis.

Physical Examination on Admission.—Height, 175 cm.; weight, 61.13 kg. Patient was a well developed but rather poorly nourished man; lips somewhat cyanotic. He showed slight dyspnea, but sat up in bed reading comfortably. There was a slight venous pulsation in the neck. Chest was of normal shape and size. There were moderate retractions of the upper left side, seen chiefly in the second and third intercostal spaces. Lungs: Marked diminution of resonance over the whole left chest, with hyperresonance of the right. The upper left chest anteriorly was almost flat and fremitus was increased. Over this area the breath sounds were somewhat amphoric in quality. Elsewhere on the left the expiration was prolonged and high pitched. Heart: There was a general heaving of the precordium. The apex impulse was of maximum intensity in the fifth intercostal space 12 cm. to the left of the midline. The cardiac dulness extended from the right sternal margin to 14 cm. to the left in the fifth intercostal space. Rhythm was regular. There were no murmurs. There was slight accentuation of the aortic second sound. Blood pressure: Systolic, 160 mm.; diastolic, 120 mm. Arteries not thickened. Abdomen was somewhat distended and tender in the right upper quadrant. Liver was felt three fingers' breadth below the costal margin. Hands were somewhat cyanotic and puffy, but did not pit. There was some edema of both lower extremities and under the sacrum.

Laboratory Examination.—The urine showed a low specific gravity (1.010), considerable albumin, no sugar, many hyalin and granular casts, many red blood cells and many clumped leukocytes. Blood: May 4, leukocytes, 10,000; hemoglobin, 70 per cent.; May 6: nonprotein nitrogen, 39.5 mg. per hundred c.c.; creatinin, 1.7 mg. per hundred c.c. May 5 the sputum contained many tubercle bacilli.

The patient improved rapidly. May 12 the dyspnea was almost gone; edema very slight. The roentgen ray showed pulmonic fields of unequal size, the right being larger than the left. There was marked diminution of the illumination throughout the entire left pulmonic field, and the middle third of the right. Costophrenic spaces were clear. There was increase in size and density of the right hilum shadow. There was increase in size, number and density of the left pulmonic and also of the middle third of the right field, markings agglutinated throughout. Large cavity at the left apex. Diaphragm shadow normal. Heart enlarged, distorted in appearance, with adhesions. Fibrosis, infiltration and cavitation of the left lung, tuberculosis.

May 24 there was no edema or dyspnea. Blood pressure: Systolic, 128 mm.; diastolic, 110 mm. Fundus of each eye normal. Comfortable.

May 25 he was studied in the calorimeter. Rectal temperature 36.7 C. His heat production was 70.7 calories per hour, or 40.5 calories per square meter per hour, being 3 per cent. above the average normal. He was then studied in the metabolism ward. The diet given is shown in Table 6 and graphically in Figure 19.

May 26 the nonprotein nitrogen content of the blood was 26 mg. per hundred c.c.

June 1, 1920, a cystoscopy was done. The cystoscope passed easily into the bladder and some clear urine was obtained. Bladder capacity normal. Bladder neck and fundus normal, but many trabeculations were seen on the posterior bladder wall. Mucosa normal. Both ureteral orifices were normal. Specimens were obtained from both sides, but no further report was made.

TABLE 6.—Diet Chart and Nitrogen Balance in Case 15

Name and Date	Total Calories	Carbohydrate, Gm.	Fat, Gm.	Food N, Gm.	Urine N, Gm.	Excreta N,* Gm.	N Balance, Gm.	Body Wt., Kg.	Urine Vol., C.c.	Water Intake, C.c.	NaCl Intake Gm.	Urine NaCl Gm.
Joseph R.												
5/15/20	1,678	165	86	9.1	9.5	10.5	−1.4	64.0	2,155	1,900	7.61	
5/16/20	1,886	182	92	10.8	10.6	11.6	−0.8	....	2,080	1,900	7.61	
5/17/20	1,823	189	85	10.0	10.7	11.7	−1.7	62.5	2,080	2,000	7.99	8.48
5/18/20	1,992	229	85	10.2	8.0	9.0	+1.2	61.8	2,210	2,224	7.45	9.57
5/19/20	2,261	277	94	10.0	8.2	9.2	+0.8	....	1,630	2,000	7.26	6.15
5/20/20	2,002	250	78	9.9	8.1	9.1	+0.8	....	1,740	2,000	7.23	6.80
5/21/20	1,914	220	86	8.2	7.6	8.6	−0.3	62.0	2,135	2,000	7.40	7.29
5/22/20	2,248	228	123	4.9	7.6	8.6	−3.7	....	2,135	2,000	7.66	7.29
5/23/20	1,908	248	92	4.6	5.6	6.6	−2.0	....	2,155	2,000	6.85	8.32
5/24/20	2,085	269	96	4.8	5.7	6.7	−1.9	62.3	2,350	2,000	6.94	9.13
5/25/20	1,772	251	67	4.6	5.1	6.1	−1.5	61.3	1,930	2,000	6.87	8.06
5/26/20	2,370	302	113	3.4	5.1	6.1	−2.7	....	2,580	2,000	6.58	11.15
5/27/20	2,510	332	114	3.3	4.3	5.3	−2.0	60.8	2,520	2,000	6.33	10.96
5/28/20	2,496	327	115	3.3	2.5	3.5	−0.2	60.4	1,480	2,000	6.54	5.50
5/29/20	2,555	342	115	3.4	4.3	5.3	−1.9	....	2,380	2,000	6.55	9.26
5/30/20	2,496	327	115	3.3	3.9	4.9	−1.6	59.4	2,455	2,000	6.54	8.59

* Estimated.

Comment.—The tendency to retain nitrogen in the blood in this case is negligible. The nonprotein nitrogen of the blood before beginning the diet was 39.5 mg. per hundred c.c., while on May 20, before the food nitrogen was reduced, the nonprotein nitrogen was only 26 mg. per hundred c.c. The explanation of the loss in weight becomes apparent at once on examination of the intake and output of salt and water. The weight declined as an excess of salt and water were eliminated, and the edema disappeared.

DISCUSSION OF RESULTS

The results of the observations made in the calorimeter are shown in Table 7. The respiratory quotients are all within normal limits. The average quotient for fasting [25] observations is 0.79, so that there is no evidence of a qualitative change in the combustions as far as the respiratory quotients are concerned.

Regarding quantitative changes in the metabolism, the data are presented from two points of view in Table 8. It is customary to compare the observed heat production of a patient with the theoretical heat production of a normal man of the same surface area. The percentage variation from the average normal metabolism is shown. It will be observed that in only ten of the fifteen cases were there observations which were considered basal; that is, in the condition of complete rest in the fasting state. The conception of the basal metabolism on which this was based implies the minimal metabolism. If the patient had fever at the time of observation it was considered basal only if the temperature was approximately at the lowest part of the diurnal variation. In the case of Robert W., the patient was very quiet at a temperature of about 40 C. This was not considered basal because the temperature was near the peak of the diurnal curve. In the first hour of the observation on Trellis H. the patient was also very quiet at a similar temperature. If one considers these as basal periods then it may be said that the basal metabolism at 40 C. is 28 or 29 per cent. above the average normal. In the ten remaining cases the basal metabolism ranges from 3 per cent. below to 15 per cent. above the average normal. Barbour's three cases lie within this range, so that it appears that the basal metabolism, as conceived above, is but very slightly elevated above that of normal men of the same surface area.

It should be remembered, however, that in losing weight the surface area of the patient has diminished. As far as each individual patient is concerned, the normal metabolism is the metabolism in health. Comparison of the present with the probable normal metabolism has been made and is also shown in Table 8, for each case in which the previous weight of the patient was known. It will be observed that in all cases except one, John S., the average hourly basal heat production observed is equal to or less than the estimated calories per hour for the same patient in health. In the case of John S. the increase is slight.

25. Not strictly fasting; small standard breakfast, previously referred to," was given. The effect of this may be considered negligible.

TABLE 7.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Chas. G.	Prelim.	12:26	....	....	....	....	....	....	....
5/8/17	1	1:26	22.2	21.0	0.77	30.5	0.30	....	62.2
52.2 Kg.	2	2:26	22.6	21.0	0.78	30.6	0.30	....	65.7
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	69.7	....
Chas. G.	Prelim.	12:10	....	....	....	....	....	....	....
5/11/17	1	1:10	23.0	20.2	0.83	28.4	0.33	....	66.3
52.7 Kg.	2	2:10	23.2	21.7	0.78	38.0	0.33	....	77.2
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	69.8	....
Chas. G.	Prelim.	11:58	....	....	....	....	....	....	....
5/14/17	1	12:58	22.5	20.2	0.81	47.7	0.31	....	73.1
52.4 Kg.	2	1:58	23.0	20.4	0.82	39.7	0.31	....	70.0
1.57 Sq. M.	3	2:58	22.9	21.3	0.78	42.7	0.21	....	73.5
	4	3:35	13.8	12.7					
	Aver.	.....	....	....	....	....	....	68.8	....
Trellis H.	Prelim.	11:47	....	....	....	....	....	....	....
5/9/17	1	12:47	29.7	26.6	0.81	40.1	0.44	98.0	78.4
51.7 Kg.	2	1:47	26.4	24.2	0.79	33.5	0.44	80.2	74.8
1.57 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Robert W.	Prelim.	11:18	....	....	....	....	....	....	....
5/25/17	1	12:18	26.3	23.7	0.81	36.5	0.57	....	72.1
53.4 Kg.	2	1:18	25.6	25.3	0.74	42.1	0.57	....	73.3
1.57 Sq. M.	3	2:18	25.2	23.1	0.80	49.4	0.57	....	93.5
	Aver.	.....	....	....	....	....	....	78.6	....
Geo. P.	Prelim.	12:07	....	....	....	....	....	....	....
5/24/17	1	1:07	23.8	21.8	0.79	32.3	0.27	72.7	66.0
58.5 Kg.	2	2:10*	25.9	23.4	0.80	32.8	0.27	78.3	69.7
1.70 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Spencer C.	Prelim.	11:41	....	....	....	....	....	....	....
12/10/19	1	12:41	22.6	18.4	0.89	28.1	....	66.8	54.8
44.3 Kg.	2	1:41	23.1	19.1	0.88	30.4	....	65.0	58.5
1.48 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	12:47	....	....	....	....	....	....	....
12/17/19	1	1:47	19.5	17.3	0.82	21.9	....	57.9	49.1
44.6 Kg.	2	2:47	19.8	18.0	0.80	21.6	....	60.2	47.3
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	8:50 p.m.	....	....	....	....	....	....	....
12/19/19	1	9:50	19.6	19.1	0.75	31.6	....	62.9	61.2
45.5 Kg.	2	10:50	23.9	21.2	0.82	31.1	....	71.2	60.5
1.53 Sq. M.	3	11:50	23.2	21.6	0.78	34.6	....	71.7	71.0
	Aver.	.....	....	....	....	....	....	....	....
Edith B.	Prelim.	2:42 p.m.	....	....	....	....	....	....	....
1/6/20	1	3:42	22.9	21.0	0.79	27.0	0.07	70.2	59.8
44.0 Kg.	2	4:42	22.2	20.6	0.78	27.9	0.07	68.9	63.7
1.53 Sq. M.	3	5:42	22.6	21.0	0.78	31.0	0.07	70.1	60.1
	Aver.	.....	....	....	....	....	....	....	....
Harry G.	Prelim.	12:38	....	....	....	....	....	....	....
1/13/20	1	1:38	23.6	21.5	0.80	29.4	....	71.8	78.2
42.8 Kg.	2	2:38	24.1	22.6	0.77	38.1	....	75.0	71.5
1.40 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Joseph D.	Prelim.	12:12	....	....	....	....	....	....	....
1/17/20	1	1:12	20.5	17.9	0.88	26.0	0.17	60.4	58.5
50.0 Kg.	2	2:12	21.8	21.0	0.76	29.8	0.17	69.3	67.9
1.74 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Michael C.	Prelim.	11:50	....	....	....	....	....	....	....
1/22/20	1	12:50	26.5	25.2	0.76	41.5	0.05	83.8	82.3
50.0 Kg.	2	1:50	25.7	23.6	0.79	42.5	0.05	79.1	81.6
1.62 Sq. M.	Aver.	.....	....	....	....	....	....	....	....

—CALORIMETRIC DATA

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	37.8	...	....	....	..	..	..	....	....	Basal
64.4	37.9	...	4.0							
67.0	37.9	...	6.5							
....	....	116	....	0.77	11	70	19	1.34	44.4	
....	38.6	...	....	....	..	..	..	....	....	Falling temperature
57.2	38.4	...	11.0							
68.6	38.2	...	18.0							
....	....	129	....	0.80	13	59	28	1.33	44.5	
....	38.1	...	....	....	..	..	..	....	....	Basal
60.4	37.8	...	2.5							
73.0	37.9	...	7.5							
70.8	37.8	...	8.9							
....	....	118	....	0.80	12	60	29	1.31	43.8	
....	39.7	...	....	....	..	..	..	....	....	Rising temperature
93.1	40.1	...	18.5	0.81	12	56	32	1.90	62.4	
78.8	40.2	...	....	0.80	15	59	26	1.55	51.1	
....	....	90								
....	40.1	...	....	....	..	..	..	....	....	High temperature, very quiet
65.9	40.0	...	2.5							
68.2	39.6	...	4.5							
80.5	39.4	...	3.0							
....	....	104	....	0.73	19	73	8	1.47	50.1	
....	37.4	...	....	....	..	..	..	....	....	(* 63 min.) Basal; very quiet; work adder broken
75.4	37.6	...	....	0.79	10	64	26			
76.6	37.8	...	....	0.80	10	60	30			
....	....	70	....	....	..	..	..	1.26	43.3	
....	36.6	...	....	....	..	..	..	....	....	Basal
57.8	36.6	...	24.2	....	..	..	..	1.42	42.4	
57.0	36.6	...	1.3	....	..	..	..	1.47	43.9	
....	....	93								
....	37.3	...	....	....	..	..	..	....	....	Basal
67.9	37.8	...	23.0	....	..	..	..	1.30	37.8	
67.0	38.3	...	23.0	....	..	..	..	1.35	39.3	
....	....	116								
....	39.5	...	....	....	..	..	..	....	....	High fever, restless in last hour, quiet in first hour
71.4	39.8	...	25.0	....	..	..	..	1.38	41.0	
65.5	39.9	...	21.0	....	..	..	..	1.57	46.5	
70.0	39.6	...	58.7	....	..	..	..	1.58	46.8	
....	....	125								
....	39.9	...	....	....	..	..	..	....	....	High temperature, coughing
68.5	40.1	...	40.0	0.79	2	68	30	1.64	47.1	
75.0	40.4	...	27.0	0.78	2	73	25	1.56	45.0	
53.1	40.0	...	33.0	0.78	2	72	26	1.60	45.8	
....	....	137								
....	39.2	...	....	....	..	..	..	....	....	Observation vitiated by restlessness
69.0	39.0	...	45.0	....	..	..	..	1.68	51.3	
69.7	38.9	...	43.0	....	..	..	..	1.68	51.4	
....	....	120								
....	37.2	...	....	....	..	..	..	....	....	Afebrile, basal, moved in last 4 min. of last period
58.2	37.2	...	39.5	0.84	8	52	40	1.02	34.7	
70.5	37.2	...	50.0	0.75	7	77	16	1.17	39.9	
....	....	82								
....	39.8	...	....	....	..	..	..	....	....	Restless, coughing
65.2	39.4	...	43.0	0.76	2	80	18	1.68	51.7	
4.4	39.2	...	36.0	0.79	2	70	28	1.58	48.8	
....	....	120								

TABLE 7.—CALORIMETRIC—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calorimetry, Cal.	Heat Eliminated, Cal.
Anna H.	Prelim.	12:25	....	....	....	....	....	....	....
2/5/20	1	1:25							
41.0 Kg.	2	2:25	45.5	47.3	0.76	62.9	0.46	143.9	138.2
1.41 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	11:50	....	....	....	....	....	....	....
2/10/20	1	12:50	21.6	20.1	0.78	37.5	....	66.8	69.0
45.5 Kg.	2	1:55*	23.9	22.7	0.73	35.3	....	77.8	71.9
1.53 Sq. M.									
John H.	Prelim.	11:54	....	....	....	....	....	....	....
2/12/20	1	12:54	24.1	23.4	0.75	34.6	0.42	76.6	71.6
45.1 Kg.	2	1:54	25.5	25.1	0.74	40.3	0.42	82.2	77.7
1.53 Sq. M.	3	2:54	26.5	26.5	0.73	43.6	0.42	86.5	81.7
	Aver.	.....	....	....	....	....	....	....	....
John H.	Prelim.	1:19	....	....	....	....	....	....	....
3/1/20	1	2:19	21.4	21.6	0.72	30.6	....	70.5	68.9
44.9 Kg.									
1.53 Sq. M.									
John H.	Prelim.	1:22	....	....	....	....	....	....	....
4/14/20	1	2:22	19.9	17.8	0.82	48.9	....	59.6	75.2
44.7 Kg.	2	3:22	20.8	20.0	0.76	47.2	....	66.3	69.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:15	....	....	....	....	....	....	....
3/2/20	1	1:15	23.0	21.5	0.78	34.9	0.34	71.2	76.6
50.3 Kg.	2	2:15	22.2	22.6	0.75	33.8	0.34	74.2	75.5
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Wm. H.	Prelim.	12:00	....	....	....	....	....	....	....
3/10/20	1	1:00	20.8	19.4	0.78	31.4	0.30	64.4	72.1
49.7 Kg.	2	2:00	21.5	20.2	0.78	30.3	0.30	66.8	70.6
1.53 Sq. M.									
Wm. H.	Prelim.	11:27	....	....	....	....	....	....	....
3/11/20	1	12:27	21.8	21.0	0.75	40.0	0.65	68.7	73.1
49.7 Kg.	2	1:27	24.0	22.5	0.77	32.4	0.65	73.9	70.5
1.53 Sq. M.	3	2:27	27.4	26.3	0.76	33.9	0.65	86.1	76.1
	Aver.	.....	....	....	....	....	....	....	....
John S.	Prelim.	12:37	....	....	....	....	....	....	....
3/17/20	1	1:37	26.9	22.9	0.86	41.4	....	77.6	83.6
62.3 Kg.	2	2:37	27.1	28.0	0.71	51.9	....	91.5	92.3
1.88 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:20	....	....	....	....	....	....	....
3/24/20	1	12:20	26.1	24.3	0.78	41.5	....	80.8	81.2
49.2 Kg.	2	1:22*	25.1	22.6	0.81	48.0	....	76.1	90.4
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Geo. M.	Prelim.	11:22	....	....	....	....	....	....	....
3/26/20	1	12:22	27.4	23.1	0.86	43.9	....	78.4	80.0
48.9 Kg.	2	1:22	25.8	23.2	0.81	61.6	....	77.5	101.6
1.53 Sq. M.	Aver.	.....	....	....	....	....	....	....	....
Joseph R.	Prelim.	12:27	....	....	....	....	....	....	....
5/25/20	1	1:27	23.5	21.2	0.81	29.7	0.20	71.0	60.5
61.3 Kg.	2	2:27	23.1	21.1	0.80	29.5	0.20	70.4	64.1
1.74 Sq. M.	Aver.	.....	....	....	....	....	....	....	....

—DATA—(*Continued*)

Direct Calorimetry Rectal Temp., Cal.	Rectal Temp., C.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg.	Per Sq. M. Linear	
....	39.4									
	39.5	...	21.0							
140.3	39.6	...	21.0	0.74	17	73	10	....	....	Fairly quiet
....	....	132	....	....	..	..	..	1.76	51.1	
....	37.4	...	....	....	..	..	..	....	....	(* 65 min.) Basal
65.2	37.3	...	8.5	....	..	..	..	1.47	43.7	
74.6	37.4	...	11.0	....	..	..	..	1.57	46.7	
....	37.9	...	....	....	..	..	..	....	....	350 gm. meat given 1 hour before start
72.0	37.9	...	30.0	0.74	15	75	10	1.70	50.0	
79.5	38.0	...	20.0	0.73	14	79	7	1.82	53.7	
84.2	38.1	...	37.0	0.72	13	57	30	1.92	56.5	
....	....	93								
....	38.7	...	....	....	..	..	..	....	....	Basal
64.6	38.7	...	18.0	....	..	..	..	1.57	46.1	
....	37.8	...	....	....	..	..	..	....	....	Basal
60.5	37.4	...	3.0	....	..	..	..	1.33	39.0	
72.4	37.5	...	11.0	....	..	..	..	1.48	43.3	
....	....	104								
....	38.6	...	....	....	..	..	..	....	....	Basal in first hour, coughing in second hour
76.3	38.6	...	18.5	0.78	13	67	20	1.41	46.5	
75.9	38.6	...	35.5	0.74	12	78	10	1.47	48.5	
....	....	80								
....	38.0	...	....	....	..	..	..	....	....	Basal
72.2	38.0	...	8.5	0.78	12	68	20	1.32	42.1	
71.0	38.0	...	11.0	0.77	12	69	19	1.49	48.5	
....	37.6	...	....	....	..	..	..	....	....	350 gm. meat given 1 hour before start
64.0	37.4	...	3.5	0.74	23	70	7	1.38	44.9	
78.3	37.5	...	14.0	0.76	20	65	15	1.49	48.3	
88.1	37.8	...	24.0	0.75	25	66	9	1.73	56.3	
....	....	86								
....	37.8	...	....	....	..	..	..	....	....	Basal
83.7	37.9	...	10.0	....	..	..	..	1.25	41.3	
69.4	37.4	...	32.0	....	..	..	..	1.47	48.7	
....	....	114								
....	39.6	...	....	....	..	..	..	....	....	(* 62 min.) Falling temperature, restless
74.5	39.4	...	25.0	....	..	..	..	1.64	52.8	
61.8	38.7	...	30.0	....	..	..	..	1.46	48.1	
....	....	94								
....	39.2	...	....	....	..	..	..	....	....	Rapid fall of temperature, restless
63.3	38.8	...	40.0	....	..	..	..	1.00	51.2	
74.2	38.2	...	40.0	....	..	..	..	1.59	50.6	
....	.. .	84								
....	36.7	...	....	....	..	..	..	....	....	Basal
62.2	36.8	...	17.0	0.81	8	60	32	1.16	40.8	
58.7	36.7	...	12.0	0.80	8	64	28	1.15	40.5	
....	....	88								

In the remaining observations, which were not basal, it will be observed in Table 8 that the heat production may be considerably increased by coughing, restlessness and by high fever. The increase in metabolism is usually due to several factors combined and it is, of course, impossible to evaluate each factor. The greatest increase in any single hour reached 43 per cent. above the average normal in the case of Trellis H., whose temperature was over 40 C. and who was coughing. In one observation on William H. the temperature remained stationary at 38.6 C. during two hours in the first of which

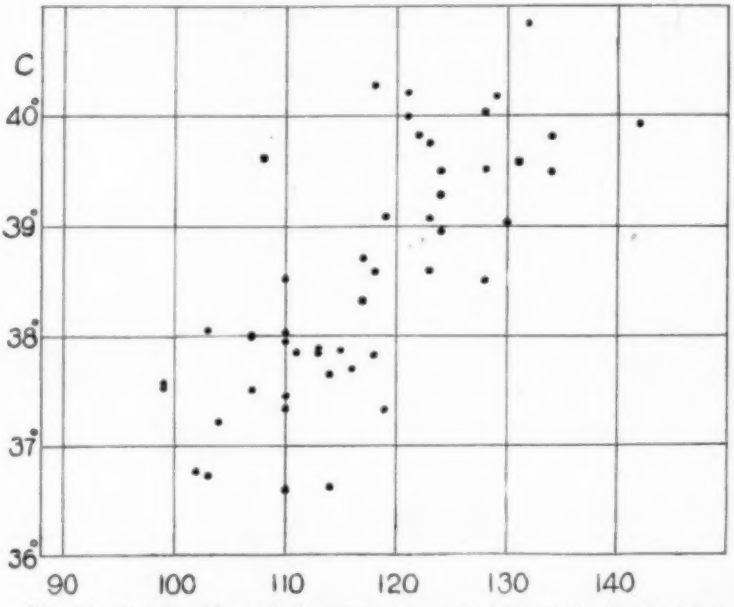

Fig. 13.—Relationship of body temperature and heat production in tuberculosis. The metabolism, during a short period, expressed in terms of percentage of average normal (100 per cent.) is plotted against the mean rectal temperature for the same period, which was usually one hour.

the patient was very quiet and the metabolism was 18 per cent. above the average normal. In the second hour he was likewise very quiet but coughed considerably, with the result that a further increase of 5 per cent. in metabolism occurred.

In Figure 13 an attempt has been made to evaluate the effect of body temperature on the heat production. In the figure the spots represent the percentage of average normal metabolism in a given period, usually one hour, plotted against the average rectal temperature for the period. The grouping of these points suggests the

general tendency of an increased body temperature to increase the heat production. In the case of Robert W. the patient was very quiet at a temperature ranging between 40.1 and 39.4 C., the metabolism being 29 per cent. above average normal. Also, in one hour Trellis H. was very quiet, with a temperature of from 40.1 to 40.2 C., his metabolism being 29 per cent. above average normal. In these two cases the effect of temperature is uncomplicated.

In Figure 14 there is a graphic representation of the relationship of heat produced in the body to the heat eliminated from the body in five cases, chosen to illustrate different phases of temperature change. In the case of Edith B., the temperature rose from 37.3 C. to 38.3 C. during two hours, without a chill. It will be observed that during this rise of 1 degree the heat production rose only a little over two calories per hour. During the first hour the heat eliminated was 9 calories less than the heat produced, and during the second hour the elimination of heat was about 2 calories less than in the first, still further increasing the storage of heat.

The question of the mechanism of temperature changes in the body is of great interest. A review of the literature on this subject will be found in a paper by Barr and Du Bois.[26] In the metabolism of malaria the rise in temperature was accompanied by a chill and a part of the rise in heat production may therefore be attributed to the muscular work of shivering. The case of Edith B., therefore, may be contrasted with the malarial paroxysm, since in her case the rise was not accomplished by a chill, nor by much increase in metabolism, the heat radiated being reduced. Referring again to Figure 14, it will be noticed that on a subsequent occasion with a much higher temperature her metabolism during the first hour showed almost no further increase over that of the first observation. During the second and third hours she was coughing and restless. These observations show that increases in metabolism due to elevation of body temperature, per se, may not be large.

In this same observation and in a subsequent one on the same patient the peak of the rise in rectal temperature was included. Though the rectal temperature had started to drop in the third hour of each experiment, the heat eliminated from the body had not yet exceeded the heat produced. Thus, it appears that for a short time, at least, the average body temperature was still rising after the rectal temperature began to fall.

The fourth observation, graphically presented in Figure 14, shows a rapid fall of temperature with sweating. Here the heat lost greatly

26. Barr, D. P., and Du Bois, E. F.: **The Metabolism in Malarial Fever**, Arch. Int. Med. **21**:627 (May) 1918.

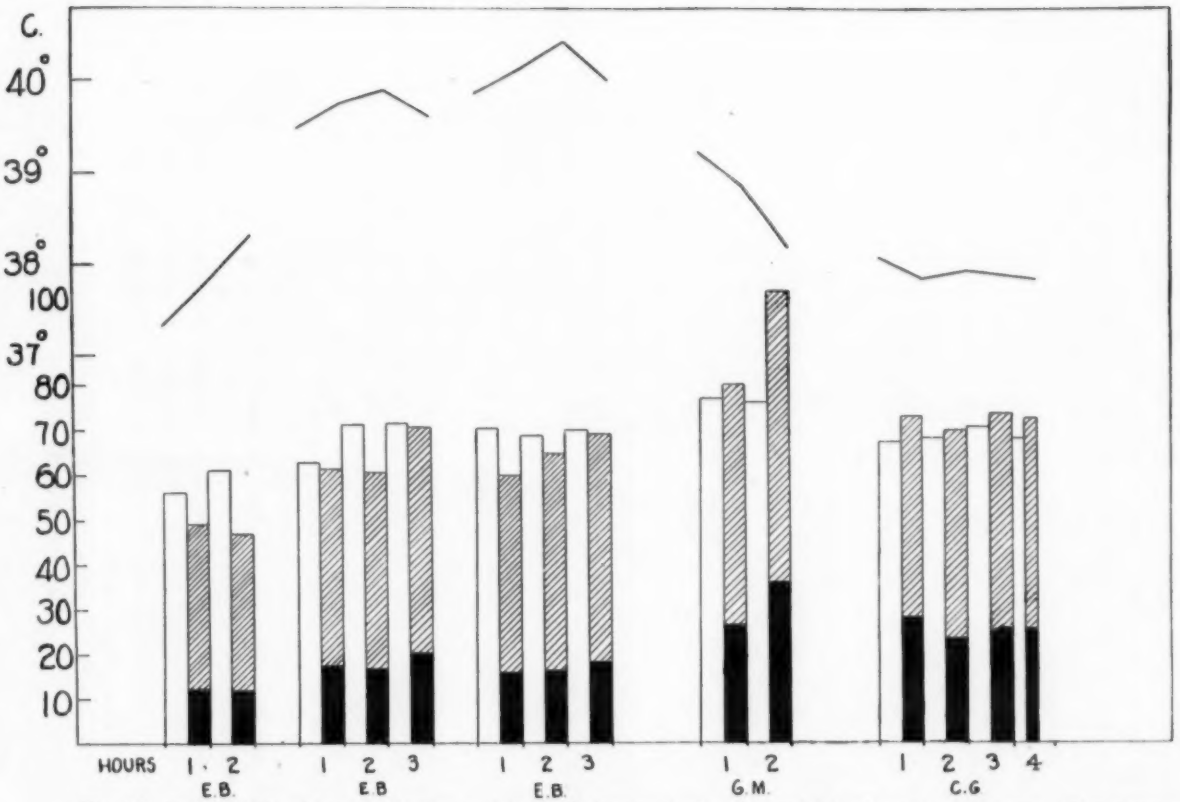

Fig. 14.—Relationship of heat production and heat elimination during rise and fall of rectal temperature. Five observations on three individuals. Lines show rectal temperature in degrees C. Unshaded columns represent calories per hour produced in the body, determined by the indirect method. Shaded columns represent heat lost from the body by vaporization of water (solid black) and by radiation (hatched). Periods are one hour for each pair of columns.

exceeded the heat produced, and the average body temperature fell with the rectal temperature. In this observation a great increase occurred in the number and percentage of calories lost by vaporization of water from the skin and lungs. Du Bois [27] has shown that under ordinary circumstances the water elimination from these sources requires about 25 per cent. of the total heat for its vaporization. In the case of George M. the percentage was between 32 and 35. In the observation of Charles G., shown in the same figure, the latent heat of vaporization amounts to 38 per cent. of the total. This observation was made at the end of a fall in temperature and it will be noted that the average body temperature continued falling after the rectal temperature had become almost stationary. These observations show that the rectal temperature is not an entirely reliable index of changes of the average body temperature and that the absolute relation between the two remains unknown.

In this connection it should be pointed out that the heat produced, as calculated in the direct calorimetry, is equal to the heat eliminated plus or minus the body change correction. This body change correction is estimated by multiplying the change in rectal temperature in degrees centigrade by the specific heat of the body (0.83) times the body weight in kilograms. For the year 1919-1920 the total number of calories measured indirectly was 6,511.73, the total heat eliminated was 6,441.60 calories, while the total heat produced measured by the direct calorimetry, corrected for changes in rectal temperature, was 6,167.37. Such a discrepancy may be accounted for partly by the lack of parallelism between the rectal and average body temperatures and the fact that the total fall in rectal temperature exceeded the total rise.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN TUBERCULOSIS

Two of the patients in this series were given a meal of meat in order to study the effect of the protein on the heat production. Various meals have been used in the past for this purpose, but in the present instance the meal consisted of 350 gm. of lean beef, ground, pressed into balls, and cooked in 10 gm. of butter. This gave 70 gm. of protein, 28 gm. of fat and 547 total calories. The observation in each case was started one hour after the middle of the meal and continued for three hours. The rise in heat production compared with the basal heat production is shown graphically in Figure 15..

The average increase in metabolism per hour for three hours was 16.1 per cent. in the case of William H. and 18.4 per cent. in

27. Soderstrom, G. F., and Du Bois, E. F.: The Water Elimination Through the Skin and Respiratory Passages, Arch. Int. Med. **19**:931 (June) 1917.

the case of John H. In the first case the extra heat in the fourth hour after eating amounted to 31 per cent. of the basal metabolism and in the second case to 25 per cent. The effect of the same meal has been studied on three normal men. So far, the behavior of the tuberculous patients has differed in no way from that of normals. Further study of the effect of this protein meal, both on tuberculous and normal subjects, will be the subject of a later communication.

With the normal subject with the same meal the average percentage increases in the second, third and fourth hours, respectively, were 16, 24 and 24 per cent. The average increase per hour was 21 per cent. There were considerable variations among the normals studied, probably due to differences in the rate of digestion and absorption. The effect of the meal has been observed on one normal to the end of the fifth hour after eating, in which the metabolism

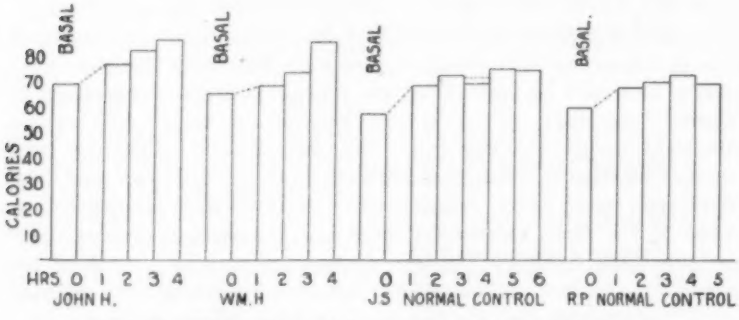

Fig. 15.—Effect of a protein meal on the heat production.

was still 30 per cent. above the basal level, with an average hourly increase of 25 per cent. It seems probable that the effect of the meal would persist for from nine to ten hours at least.

It is to be remembered that Coleman and Du Bois [28] found very little specific dynamic action of protein in febrile typhoid patients. They point out that the protein metabolism was at high level at the time of the basal observation, due to the influence of the disease, and that the protein ingested merely served to replace protein already breaking up in increased quantity, and such protein would not serve to increase the heat production. The fact that a specific dynamic rise has been noted in tuberculosis is further evidence that the toxic destruction of protein is less than in typhoid fever.

28. Coleman, Warren, and Du Bois, E. F.: Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, Arch. Int. Med. **15**: Pt. 2, 940 (May) 1915.

THE PROTEIN MINIMUM IN TUBERCULOSIS

The minimum protein requirement in tuberculosis probably depends, as in health, on the size of the "wear and tear" quota and an adequate supply of nonprotein foodstuffs. Investigations of other infections have shown generally an increase in protein destruction due to the toxins of the disease. Some evidence [2] has been given regarding the extent of this toxic destruction, which indicates that it is small but of importance because of the great duration of the disease.

The work of Chittenden, Sivén, Kumagawa and many others [29] indicates that the protein metabolism of normal men may be reduced to a very low level. More recently Sherman [30] has found from 0.633 to 0.637 gm. of protein per kilogram of body weight per diem to be adequate for the maintenance of normal men.

In typhoid fever Kocher [31] has studied the toxic destruction of protein by giving to a patient a diet containing carbohydrate in large amounts and very little protein. He found it impossible, during the febrile period, to reduce the protein metabolism to the low level of the normal "wear and tear" quota.

In four of the cases of our series, observations were made which were somewhat similar to those of Kocher. The estimated daily basal requirement for each case is given in Table 8. The records of the amounts of food given and of the nitrogen balances are to be found in Tables 3 to 6, inclusive, and are shown graphically in Figures 16 to 19, inclusive. In general, the procedure was to give the patient a diet slightly in excess of the basal energy requirement, containing between 10 and 15 gm. of nitrogen per diem for a period of five or six days. The nitrogen intake was then reduced, with a simultaneous increase in the amount of fat and carbohydrate.

The data obtained in these four cases are insufficient to establish the minimum requirement of protein for tuberculous patients. They will serve as a starting point for work of a similar nature, on which a later report will be made. In general it may be said that when the food nitrogen was reduced to the low level of from 3 to 3.5 gm. per diem, with the addition of from 600 to 900 calories to the basal requirement, the urinary nitrogen excretion fell to the level of 5 or 6 gm. per diem, the patient remaining in negative nitrogen balance. This indicates a "wear and tear" quota greater than normal. The minimum nitrogen excretion noted by Kocher [31] in a typhoid patient was somewhat higher (10.4 gm. during fever, from 5.8 to 6.7 gm. beginning convalescence) and was obtained at the expense of much

29. Chittenden, Russell H.: Physiological Economy in Nutrition, 1914.
30. Sherman, H. C.: Protein Requirement in Maintenance of Man, J. Biol. Chem. **41**:97, 1920.
31. Kocher: Deutsch. Arch. f. klin. Med. **115**:106, 1914.

more carbohydrate and fat. A toxic destruction of protein exists, therefore, in tuberculosis but to less extent than in typhoid fever.

In view of the results in these four cases, it seems probable that many febrile, tuberculous patients may be kept in nitrogen balance on diets containing from 60 to 70 gm. of protein per diem. The

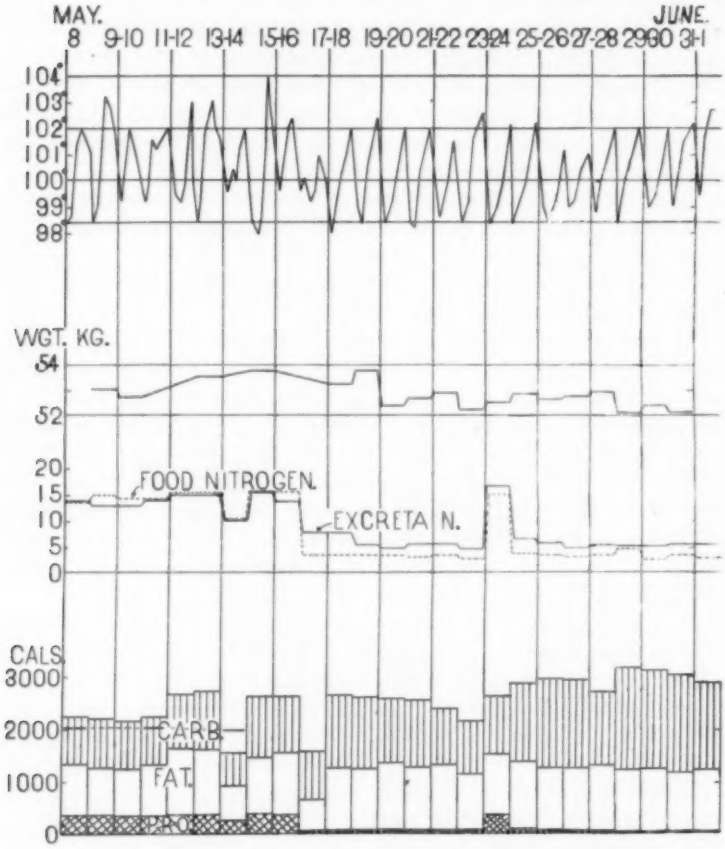

Fig. 16.—Diet chart and nitrogen balance, Charles G.

amount of protein is much less than Voit's standard allowance (118 gm.) for normal men, though somewhat greater than the normal minima of Chittenden and of Sherman (from 35 to 45 gm.). It is much less than is fed to patients in many of the sanitaria for tuberculosis.

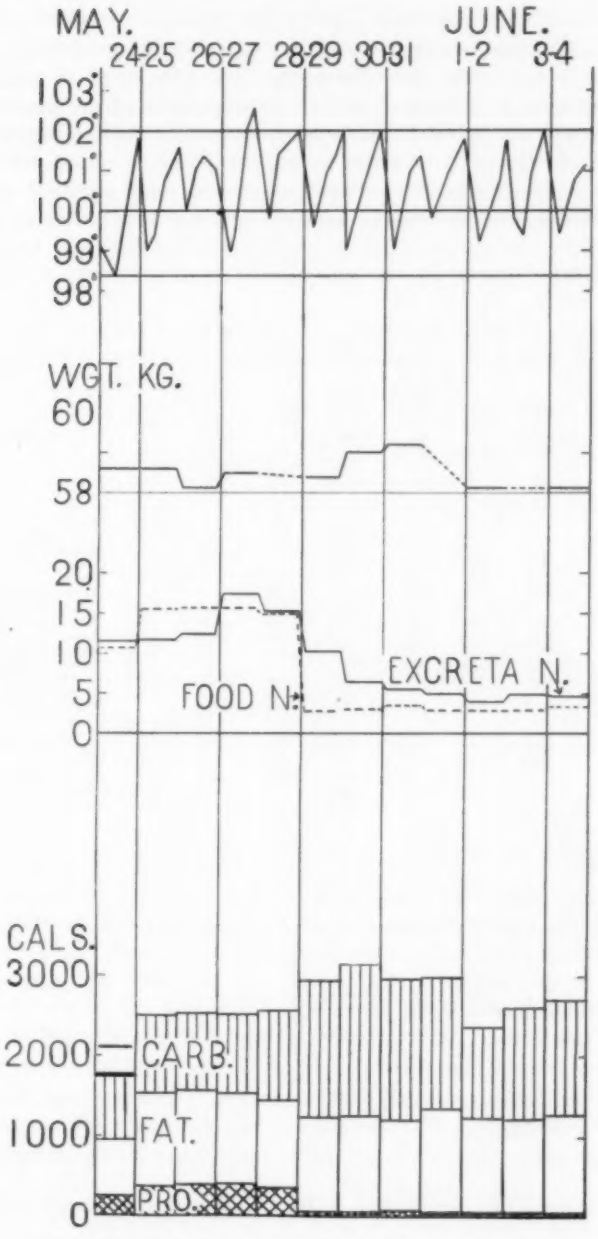

Fig. 17.—Diet chart and nitrogen balance, George P.

PRACTICAL CONSIDERATIONS REGARDING DIET IN TUBERCULOSIS

The importance of rest during periods of activity of pulmonary tuberculosis has been generally recognized. By artificial pneumothorax, by rest, by control of the cough, the volume of the respiratory exchange and of the total ventilation is reduced. This seems to be a desirable end for which to strive during the period of encapsulation of the foci of the disease. It does not seem to have occurred to the practitioner that an increase in metabolism due to the specific dynamic action of protein will have the same effect on the respiratory exchange as a similar increase due to muscular work.

TABLE 8.—SUMMARY OF CALORIMETER DATA

Name	Weight in Health, Kg.	Surface in Health, Sq. M.	Estimated Calories per Hour in Health	Present Calories per Hour Observed	Present Surface Area, Sq. M.	Metabolism Variation from Aver. Normal per Cent.	Calories per 24 Hours	Remarks
Chas. G.	....	....	. ..	69.5	1.56	+13	1,668	Basal
Trellis H.	....	....	....	84.4	1.57	+35	2,026	Fever, 40 C.; cough
Robert W. ...	....	....	....	78.6	1.57	+29	1,886	40.1-39.4 C., quiet
Geo. P.	69.5	1.84	75.4	75.5	1.70	+11	1,812	Basal
Spencer C. ...	74.0	1.85	71.2	63.9	1.48	+12	1,534	Basal
Edith B.	61.5	1.77	66.4	59.0	1.58	+ 2	.....	Basal, afebrile
				66.6	1.53	+15	1,598	Fever, restless
Harry G.	56.0	1.60	68.8	73.5	1.40	+21	1,746	Fever, restless
Joseph D.	61.3	1.75	67.4	64.9	1.74	— 3	1,558	Basal
Anna H.	51.0	1.55	62.0	72.0	1.41	+28	1,728	Fever, coughing
Mich. C.	59.0	1.74	68.7	81.5	1.62	+27	1,956	Fever, coughing
John H.	64.5	1.78	70.3	60.9	1.53	+15	1,678	Basal, febrile
				63.0	1.53	+ 5	1,512	Basal, afebrile
Wm. H.	61.0	1.67	66.0	65.6	1.54	+ 9		Basal, 38 C.
				72.7	1.53	+21	1,656	Coughing, 38.6 C.
John S.	78.0	2.04	80.6	84.6	1.86	+14	2,030	Basal
Geo. M.	62.3	1.69	66.8	77.6	1.53	+28	1,862	Fever, restless
Joseph R.	82.0	1.96	78.4	70.7	1.74	+ 3	1,697	Basal
J. D.	....	....	....	61.8	1.50	+ 4	1,483	H. G. Barbour's case
G. G.	....	....	....	62.4	1.54	+ 3	1,506	Same
S. L.	....	....	....	67.2	1.62	+ 4	1,613	Same

* Average of two operations.

During periods of acute activity of the disease it may be well to limit the protein intake and the total calories fed to patients to the minimum necessary to maintain nitrogen equilibrium without regard to the weight of the patient. Later, when acute symptoms have subsided, and when there is evidence that the natural barriers against the disease are established, a more liberal diet could be given with less fear of the effects of an increased respiratory activity.

An excellent article has just appeared, by Janney and Newell,[32] on the relationship of tuberculosis and diabetes. These authors point out that the course of pulmonary tuberculosis, complicating

32. Janney, N. W., and Newell, R. R.: Treatment of Diabetes Complicated by Pulmonary Tuberculosis, J. A. M. A. **75**:153 (July 17) 1920.

diabetes, does not seem to be influenced unfavorably by the state of undernutrition resulting from a rigid adherence to the proper diabetic diets, but quite the reverse. They show that among diabetic patients the mortality rate from tuberculosis has diminished markedly since the inauguration of the Allen treatment. Similar experience has also been recorded by Joslin.[33] In their own series of cases the development of tuberculosis seems always to have commenced during periods in which diabetic patients were living on a liberal and uncontrolled dietary. In view of these facts no unfavorable results are to be expected from temporary dietary restrictions in nondiabetic tuberculous patients.

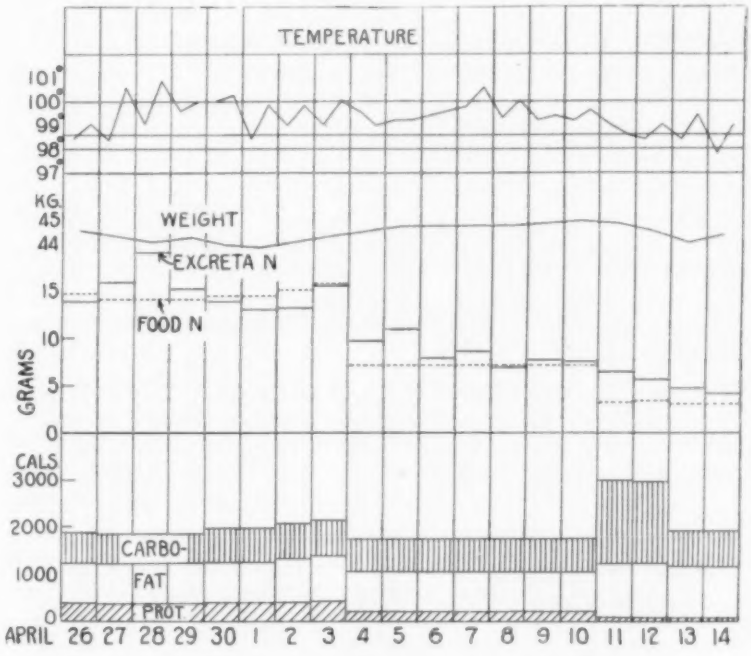

Fig. 18.—Diet chart and nitrogen balance, John H.

In Table 8 estimates of the daily heat production of patients in this series are given. These range from 1,500 to 2,000 calories per day for rest in bed and the fasting state. During periods of activity of a pulmonary tuberculosis the diet need not contain more than 500 calories above the basal requirement (from 2,000 to 2,500 calories), nor more than 60 gm. of protein. The object of such a diet is to maintain the respiratory activity at the lowest level compatible with

33. Joslin: The Treatment of Diabetes Mellitus, 1916.

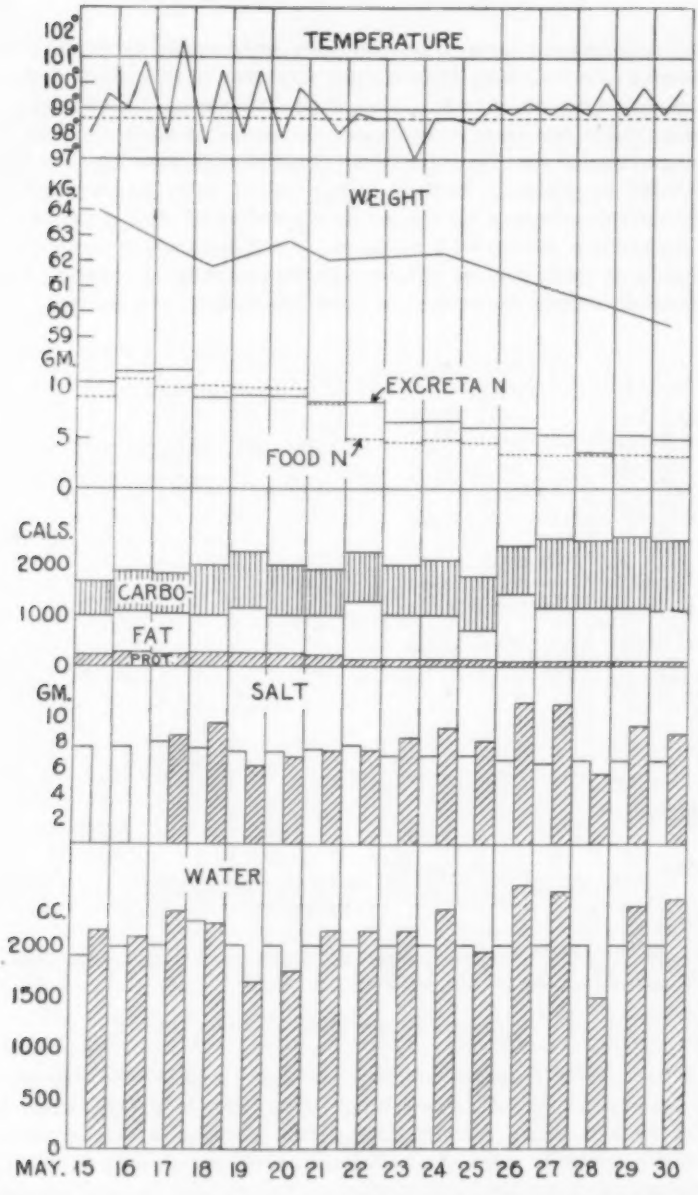

Fig. 19.—Diet chart and nitrogen balance, Joseph R. Water formed by combustion and that eliminated from skin and lungs was not included in the measurement of water balance. Water and salt output in shaded columns. Intake unshaded.

the maintenance of nitrogen equilibrium. To achieve this purpose it is just as necessary not to overfeed as it is to maintain muscular rest.

When the activity of the disease has subsided the total calories in the diet should be raised to meet the requirements of the patient as his muscular activity increases. The protein intake could also be increased to enlarge the repair quota.

SUMMARY

1. The basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. Thus, in ten cases, the variation from average normal was from minus 3 to plus 15 per cent.

2. Further increases in metabolism occur with a rise of body temperature. These increases are not large. Thus one case was given in which the temperature rose 1 degree C. during two hours without a chill. The heat production of the second hour was only two calories greater than that of the first hour. With a rectal temperature of 104 F., (40 C.) the metabolism may be 30 per cent. above the average normal.

3. The basal heat production in tuberculosis may be less than the normal for the same patient when in health; in other words, the loss in weight may be accompanied by a reduction in metabolism which more than compensates for the tendency to increase caused by the disease.

4. Limited data regarding the nitrogen excretion show that, while a toxic destruction of protein does exist in tuberculosis, it is not large. The urinary nitrogen may be reduced to from 5 to 6 gm. per diem, though nitrogen balance may be attained only at a higher level (about 10 gm. a day).

5. The specific dynamic rise in metabolism produced in two cases by the ingestion of a protein meal corresponded closely with that produced by the same meal in three normal men.

CONCLUSIONS

In view of the fact that the food requirements of tuberculous patients are not large, either as regards total energy value or nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as in normals it may be well to limit the protein intake during periods of activity (of the disease) in order to put the lungs at rest.

THE FAILURE OF ANTIBODY FORMATION IN LEUKEMIA *

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CHICAGO

A few reported studies on the blood of leukemia patients show that antibodies either do not occur or are lessened in several of the infectious diseases and after inoculation with various organisms.

Moreschi [1] observed that a patient with chronic lymphatic leukemia, who contracted typhoid fever, failed to develop agglutinin for *B. typhosus*. From a study of the literature on typhoid fever, he found that about 6.7 per cent. of typhoid fever patients normally failed to produce agglutinin. In order to determine whether the failure in antibody production in his patient was due to this normal percentage of failure or to the chronic leukemia, he started inoculating his leukemic patients against *B. typhosus* to observe the agglutinin response. In the course of two years he had inoculated two patients with lymphatic leukemia and six with myelogenous leukemia. A lymphatic leukemia patient who contracted typhoid fever and a lymphosarcoma patient with a paratyphoid B. infection also came under his observation during this time. Six of the eight vaccinated patients had no rise in temperature or any of the usual systemic symptoms occurring after typhoid inoculation. The remaining two patients had received roentgen-ray treatment, and they had slight rise in temperature, headache and malaise. In each of the vaccinated cases, the blood was tested for agglutinin before inoculation and again from eight to ten days after inoculation. One of the patients who had had a rise in temperature and one who had been under benzol and roentgen-ray treatment had agglutinin in a 1:20 serum dilution. The other six patients gave no evidence of agglutinin formation. Blood from the chronic lymphatic leukemia patient with typhoid fever and from the lymphosarcoma patient with paratyphoid B. infection had slight agglutinin in 1:10 serum dilution, but none in higher serum dilution.

Rotky [2] used a harmless vibrio which was isolated from water and which in animal experiments showed good agglutinin production. The

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* From the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital, Chicago.

1. Moreschi, C.: Ueber antigene und pyrogene Wirkung des Typhusbacillus bie leukämischen Kranken, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **21**: 410, 1914.

2. Rotky, H.: Fähigkeit von Leukämikern Antikörper zu erzeugen, Zentralbl. f. inn. Med. **35**:953, 1914.

action of this organism, one-tenth loop of killed agar culture emulsion injected subcutaneously, was tested on normal and leukemic persons. Eight normal persons tested had a slight local reaction only. One week after inoculation, however, agglutinin was present in a 1:20 serum dilution in all instances, and in a few it rose to 1:500. The one lymphatic leukemia patient and the one myelogenous leukemia patient had severe local reactions of three days' duration. They had slight fever, headache and splenic pain, which was more marked in the myelogenous leukemia patient. The leukocytes were increased in the lymphatic leukemia patient from 16,800 to 35,000, and in the myelogenous leukemia patient from 96,000 to 130,000. One week after injection of the vibrio vaccine, neither case showed any agglutinin in 1:10 serum dilutions.

EXPERIMENTAL OBSERVATIONS

Because of its bearing on the general problem of antibody formation, a more detailed study of the antibodies in a lymphatic leukemic patient and a myelogenous leukemic patient was undertaken. Each patient was inoculated with 0.5 c.c of a triple vaccine [3] containing 1,000 million *B. typhosus*, 750 million *B. paratyphosus* A and 750 million *B. paratyphosus* B per c.c. The blood count and the opsonin and agglutinin for each bacterial species were examined before vaccination and at intervals thereafter.

Agglutinin was examined by the microscopic method. Hanging drops containing suspensions of living organisms and active serums in varying dilutions were incubated 10 minutes at 37 C. before examination for clumping.

Opsonin was estimated by diluting the serum to the point of opsonic extinction. The dilution in which fifty leukocytes had the same per cent. of cells taking part in phagocytosis as a normal control with salt solution was considered the point of extinction. Varying dilutions of active serum, human leukocytes and living bacteria were incubated in capillary tubes at 37 C. for ten minutes. A film was made from each tube and the number of leukocytes taking part in phagocytosis was observed.

The case of lymphatic leukemia was a patient of Dr. C. A. Elliott, to whom we wish to express our appreciation for the privilege of studying the case. This patient was receiving roentgen-ray treatment at the time of vaccination, and radium treatments were started on the twentieth day after inoculation with triple vaccine. The patient had

3. Dreyer, G.; Gardner, A. D.; Gibson, A. G., and Walker, E. W. A.: Prophylactic Triple Inoculation Against Typhoid and Paratyphoid Fevers, Lancet **1**:498, 1918.

no rise in temperature, headache or other systemic reactions. There was slight redness and swelling at the site of inoculation, and moderate axillary glandular involvement. The white blood count (Table 1) was taken on the day of inoculation and on the fourth, eighth, twelfth, twenty-first and twenty-fifth days thereafter. There was a gradual decline in leukocytes from 325,000 to 228,000. About 99 per cent. of the white cells were small lymphocytes.

TABLE 1.—Lymphatic Leukemia

Days After Inoculation With Triple Vaccine	White Blood Count	Agglutinin			Opsonin		
		B. Typhosus	B. Paratyphosus A	B. Paratyphosus B	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
0	320,000	0	0	0	0	0	0
4	286,000	0	0	0	0	0	0
8	280,000	0	0	0	0	0	0
12	275,000	0	0	0	0	0	0
21	230,000	0	0	0	0	0	0
25	228,000	0	0	0	0	0	0

0 = no agglutinin or opsonin in undiluted serum.

Opsonin and agglutinin for *B. typhosus*, *B. paratyphosus* A and *B. paratyphosus* B were observed on the same days that the leukocyte counts were made. At no time did even undiluted serum show the presence of agglutinin or opsonin.

A healthy person injected at the same time with a similar dose of the triple vaccine, had a moderate local reaction, headache and a feeling of malaise, lasting twenty-four hours but no rise in temperature. In this person agglutinin and opsonin were present in high serum dilutions after the twelfth day.

The patient with myelogenous leukemia, who was admitted to the medical service of Michael Reese Hospital, had received no treatment at the time of vaccination. There was a moderate local reaction, one degree rise in temperature, but no other general symptoms. The leukocyte count, agglutinin and opsonin were observed on the day of inoculation and on the second, fourth, seventh, tenth, fourteenth, eighteenth and twentieth days after vaccination. The leukocyte and differential blood counts (Table 2) varied slightly from day to day but were apparently not affected by the vaccine. Undiluted serums agglutinated *B. paratyphosus* A and *B. paratyphosus* B very slightly, but never clumped *B. typhosus*. The point of opsonic extinction, using undiluted serum, was never above the normal salt control, and frequently fewer leukocytes were phagocytic.

A healthy person vaccinated at the same time had a severe local reaction lasting five days, a rise of one degree in temperature, severe

headache and general malaise of two days duration. Agglutinin and opsonin were present in this serum after the tenth day.

DISCUSSION

The results obtained in these two cases correspond to those of Moreschi and of Rotky in that no agglutinin was produced after typhoid vaccination. In addition, opsonin, not investigated by these workers, was absent. A frequent cause of death in both forms of leukemia is intercurrent infection, fatal sepsis due to the more common pyogenic bacteria being not unusual. The resistance of a leukemic person to bacterial invasion appears to be lower than that of a normal person, and this condition may find its explanation in a loss of ability on the part of the leukemic patient to form antibodies.

TABLE 2.—MYELOGENOUS LEUKEMIA

Days After Inoculation With Triple Vaccine	White Blood Count	Differential Blood Count						Agglutinin			Opsonin		
		P.	L.	T. and L. M.	E.	B.	M.	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B	B. Typhosus	B. Paratyphosus A	B. Paratyphosus B
0	42,200	34	9	28	0	0	29	0	0	0	0	0	0
2	42,000	36	7	28	0	0	29	0	0	0	0	0	0
4	42,100	38	2	29	1	5	25	0	S	S	0	0	0
7	37,100	52	2	15	1	0	30	0	S	S	0	0	0
10	42,700	54	10	7	0	0	29	0	S	0	0	0	0
14	56,000	47	7	18	0	0	28	0	S	0	0	0	0
18	36,200	54	14	7	0	0	23	0	S	0	0	0	0
20	43,000	71	2	9	0	S	18	0	S	S	0	0	0

P. = Polymorphonuclear leukocytes.
L. = Lymphocytes.
T. and L. M. = Transitionals and large mononuclears.
E. = Eosinophils.
B. = Basophils.
M. = Myelocytes.
0 = No agglutinin or opsonin in undiluted serum.
S = Slight agglutinin in undiluted serum.

While the prognosis of an infection developing during the course of leukemia is bad, the effect of the infection on the leukemia may be the reverse. It is, perhaps, improper to say that there is any actual improvement in the patient's condition or that his probable duration of life is prolonged by the intercurrent infection if he recovers from the latter, but there may be symptomatic improvement in that the high leukocyte count may be considerably or markedly decreased, an improvement comparable to that brought about by the action of leukocytotoxic agents. This phenomenon has been described by a number of observers, and in a few cases it has been associated with perceptible decrease in the enlarged lymph nodes and spleen. Possibly, the decrease in the leukocyte count may be the result of exhaustion of the hematopoietic tissues by the continuous proliferative process which is characteristic of leukemia, so that these tissues are no longer

able to meet the added stimulus of an acute infection. Or the involved tissues may be so abnormal as to be unable to respond to the stimulus in a normal manner. All cases of leukemia do not show this absence of leukocyte increase. Some patients respond to intercurrent infection with an increase in leukocytes, and Rotky's two vaccinated patients showed marked leukocytic increase; in the lymphatic leukemia patient from 16,800 to 30,000, and in the myelogenous leukemia patient from 96,000 to 130,000. Definite experimental evidence on the reason for the variable leukocytic reaction is not yielded by the cases studied, although in neither case is there the increase in leukocytes that usually follows injection of typhoid vaccine in normal persons. On the contrary, the leukocyte count in the case of lymphatic leukemia is a progressively decreasing one, a decrease which simulates that which may occur during an intercurrent infection. But this patient was under roentgen-ray treatment, and it is safer to conclude that this, rather than the vaccine injection, was the cause of the change noted. The patient with myelogenous leukemia, who had been untreated, shows a decrease on the seventh and eighteenth days, respectively, after injection of the vaccine, but this is so slight as to be most probably only part of the fluctuation in leukocytes which this patient showed while under observation. While neither case, therefore, showed such a decrease in the number of leukocytes following vaccine injection as is sometimes associated with infection, the fact that the normal increase did not occur is of importance and indicates an inability of the blood forming tissues to react to the stimulus of the injection.

The failure of agglutinin formation, both following spontaneous typhoid and paratyphoid fever, as noted by Moreschi, and following antibacterial vaccination, as noted by Moreschi and Rotky, and the absence of both opsonins and agglutinins following antityphoid vaccination in the two cases here reported, is probably part of the still unsolved problem of the locus of antibody formation. Experimental work on the negative side of this problem indicates, as has been long held but never absolutely proven, that anticellular antibodies are produced in the hematopoietic tissues, and more especially in that tissue one of whose functions is the formation of polymorphonuclear leukocytes, namely, the bone marrow. Hektoen [4] and Simonds and Jones [5]

4. Hektoen, L.: The Influence of the Roentgen Ray on the Production of Antibodies, J. Infect. Dis. **17**:415, 1915. Further Studies on the Effects of the Roentgen Ray on Antibody Production, J. Infect. Dis. **22**:28, 1918. Influence of Thorium X on Antibody Formation, J. Infect. Dis. **26**:30, 1920. Further Observations on the Effects of Roentgenization and Splenectomy on Antibody Production, J. Infect. Dis. **27**:23, 1920.

5. Simonds, J. P., and Jones, H. M.: The Influence of Exposure to Roentgen-Rays on the Formation of Antibodies, J. M. Res. **33**:183, 1915. The Effect of Injections of Benzol on the Production of Antibodies, ibid. **33**:197, 1915.

have shown that the roentgen ray, benzol and other agents which cause a pronounced decrease in the circulating leukocytes, most probably through destructive action on the hematopoietic tissues, markedly decrease or completely set aside the formation of antibodies. This is strong evidence, in a negative way, in favor of the view, propounded by Metchnikoff and strongly supported by the French school of immunology, that antibodies are formed in the hematopoietic tissues.

But proof on this point from the positive side has been more difficult to adduce, and there is still question in the minds of some as to whether antibodies are formed by leukocytes and by the tissues from which they come. Bedson [6] showed that injection of nuclein increased the phagocytic activity of the leukocytes. This reaction was fleeting and persisted only during the period of hyperleukocytosis. Tunnicliff [7] found that the leukocytes of aleuronat exudate are more highly phagocytic than those of the circulating blood, and gave as the probable explanation of this effect the younger condition of the exudate leukocytes. More recenly [8] she has shown that injection of leukocytic extract, which causes a hyperleukocytosis, increases the phagocytic activity from twofold to fourfold during the period of hyperleukocytosis.

Hyperleukocytosis and increased phagocytosis with intracellular digestion of the engulfed bacteria might, theoretically, have two diametrically opposite effects on antibody formation. If phagocytic cells are themselves capable of producing antibodies, as originally claimed by Metchnikoff, an increase in their phagocytic activity might lead to an increased secretion of antibodies, by stimulation of the normal mechanism. Bachmann [9] claims to have demonstrated the presence of specific antibodies within leukocytes after typhoid immunization of rabbits. If, on the other hand, the property of antibody formation resides, not in the circulating phagocytes, but in the hematopoietic tissues themselves, the excessive destruction of the antigen in the circulating blood might inhibit or decrease antibody formation by destroying the stimulating substances before they reach the fixed tissues. Stenström's [10] experiments support this view. The injection of normal rabbit leukocytes into a second rabbit leads to hyperleukocytosis and

6. Bedson, S. P.: Analysis of the Effect of Nuclein and Nucleic Acid on the Normal Antibody, J. Path. & Bact. **19**:191, 1914.

7. Tunnicliff, R.: Observations on the Phagocytic Activity of the Leukocytes in Exudates, Tr. Chicago Path. Soc. **8**:108, 1911.

8. Tunnicliff, R.: The Action of Leukocytic Extracts on the Phagocytic Activity of Leukocytes, J. Infect. Dis. **26**:447, 1920.

9. Bachmann, A.: Presence de substances specifiques dans les leucocytes des animaux immunises, C. R. Soc. Biol. **82**:1031, 1919.

10. Stenström, O.: Ueber die einwirkung des exsudatleukocyten auf die Antikörperbildung, Ztschr. f. Immunitätsforsch. u. Exper. Therap. **8**:483, 1911.

increased phagocytosis. When leukocytes and typhoid bacterial antigen were injected at the same time by Stenström, the formation of agglutinin and bacteriolysin was decreased or prevented.

In the acute infectious diseases hyperleukocytosis and hyperplasia of the hematopoietic tissues are associated with an increase in antibodies in the circulating blood. On a priori grounds the great increase in the number of circulating leukocytes and the marked hyperplasia of the blood forming tissues in leukemia should be associated with antibody increase during acute infection or after bacterial immunization. The opposite has been found to be the case by Moreschi and by Rotky and in the two cases here reported. Moreschi considers two possibilities in explanation of the failure of antibody formation. The first is that the large number of circulating leukocytes may change the antigen, so that its antibody inciting properties are lost before it reaches the tissues which produce antibodies. Against this possibility he placed the fact that no agglutinins were demonstrable in lymphatic as well as in myelogenous leukemia. According to the second possibility, the hematopoietic system, which is held to be the site of antibody formation, is so severely damaged in leukemia that its power to produce antibodies is lost. Stentsröm's experimental work would give strong support to the first possibility if it could be shown that the leukocytes of leukemia have the property, under the conditions which exist in the body in the disease, of taking up and destroying the injected bacteria. In both the cases which form the basis of this report, there was complete absence of opsonin even in undiluted serum. Change in the antigen brought about by the large number of circulating leukocytes before the antigen can reach the site of antibody formation must, therefore, be discarded as an explanation of the failure of antibody formation in leukemia.

Absence of antibodies in leukemia would appear to be due to the profound alterations which the hematopoietic system undergoes in the disease. The nature of the pathologic process which brings about these alterations is not yet understood, but in a number of respects the process suggests a neoplastic condition. Even if the neoplastic nature of the process is not accepted, the rate of proliferation in the hematopoietic tissues is so great that the phenomenon which Adami considers so characteristic of malignant tumors, namely, the loss of the habit of function and the assumption of the habit of growth, which after all is merely an expression of rapid proliferation, must have great influence on the functional capacities of the hematopoietic tissues and of the cells derived from them. If antibody formation is one of the functions of these tissues, then it is fair to assume that this function is greatly interfered with or set aside by the proliferative

process which characterizes leukemia. Tunnicliff's conception that the increased phagocytosis of aleuronat exudate leukocytes is due to their younger condition, is not opposed to the view stated, because these leukocytes have been produced by the action of a normal mechanism and not by a process so abnormal as that which is present in leukemia. The failure of the highly abnormal hematopoietic tissues of leukemia to produce antibodies is further evidence, again in a negative way like the action of the roentgen ray and benzol, that the normal site of antibody formation is in the blood forming tissues. When the abnormal proliferation of leukemia is more or less completely inhibited by the roentgen ray, benzol, or otherwise, then the patient may respond with more nearly normal reactions. Two of Moreschi's vaccinated patients under roentgen-ray treatment agglutinated typhoid bacilli in a 1:20 serum dilution and several reacted with a rise in temperature. The patient with lymphatic leukemia whose case is reported here was under roentgen-ray treatment, but there was no formation of agglutinin or opsonin. This failure of antibody production cannot be attributed to the roentgenization. Whereas, the roentgen ray in a normal animal interferes with antibody formation through its destructive action on the hematopoietic tissues, in a leukemic individual it should aid in antibody formation, as Moreschi found to be the case to a slight degree, through inhibition of the excessive proliferation of the same tissues.

Moreschi attempts to correlate the absence of temperature reaction after bacterial vaccination with the failure of antibody formation. The untreated patients vaccinated by him formed no agglutinin and had no rise in temperature, while several of his patients under roentgen-ray treatment had a slight temperature rise that was either delayed or of short duration. The leukemic patients vaccinated by Rotky with the water vibrio had slight fever. Of the two cases described here, the untreated myelogenous leukemia patients had a rise in temperature of one degree, the same temperature reaction that was shown by the healthy person used as a control, while the lymphatic leukemia patient who was under treatment, had no rise in temperature. It would seem, therefore, that the temperature reaction in leukemia after vaccination is variable and is not necessarily dependent on the antibody reaction. In the normal individual the temperature increase which follows the injection of a bacterial vaccine may be the expression of the increased metabolism and of the chemical changes which result in the formation of antibodies. But in leukemia, in which irregularities in the temperature curve are not unusual, the rise of temperature which may follow the injection of a bacterial vaccine need not be associated with antibody formation and may be the effect of an action on some factor other than that concerned in the production of antibodies.

SUMMARY

Individuals with leukemia who contract typhoid or paratyphoid infection may fail to develop the specific agglutinins in the blood.

A similar failure of agglutinin formation also occurs when a leukemic individual is injected with typhoid vaccine in a dosage which causes agglutinin formation in a normal control.

Opsonins are also absent in the blood after injection with typhoid vaccine.

The failure of both opsonin and agglutinin formation after typhoid vaccination, as shown in the two cases reported here, of agglutinin formation in Moreschi's spontaneously infected cases and in his vaccinated cases, and of agglutinin production after vaccination with still another bacterial species, as shown by Rotky, may indicate that the tissues of the leukemic individual have lost the property of antibody formation in general.

The loss of ability to form antibodies is probably the result of the marked alterations in the hematopoietic tissues which characterize leukemia. This loss of ability may be due to the excessive proliferation of the hematopoietic tissues, one of whose normal functions is the formation of antibodies. With rapidly repeated cell generations the cellular energy used in multiplication prevents the utilization of the energy which is necessary for normal function.

The temperature reaction after bacterial vaccination in leukemia is variable. When a rise in temperature occurs, it may not be associated with antibody production.

The leukocytic reaction after vaccination is also variable. Some cases react like normals with an increase in the number of circulating leukocytes. Others show no changes. In still others a decrease may occur. The variable leukocytic reaction, like the failure of antibody formation, is probably the result of the alterations in the hematopoietic tissues.

PRIMARY MESOTHELIOMA OF THE PLEURA

A CLINICAL AND PATHOLOGIC CONTRIBUTION TO PLEURAL MALIGNANCY, WITH REPORT OF A CASE *

ERNEST S. DU BRAY, M.D., AND F. B. ROSSON, M.D.

SAN FRANCISCO

Primary neoplasms of the pleura are among the very rare tumors. They occur considerably less frequently than primary growths of the lung or bronchi. Clinically and pathologically the malignant tumors of the pleura form the most interesting and important group. The pathogenesis and consequently the nomenclature of these tumors is still in confusion. Wagner,[1] in 1870, described the classical pleural tumor under the name "tuberkelaehnliche lymphadenome," which opened a long controversy. Schultz,[2] in 1875, reexamined the preparations of Wagner and gave a complete description of the above tumor, emphasizing the neoplastic nature of the growth and naming it "endothelial cancer." These two papers mark the beginning of a stubborn contention which, fifty years after its inception, still remains unsettled. Among the other designations which have been used to describe malignant pleural tumors may be mentioned: lymphangitis proliferans (Fraenkel, Schweninger); lymphangitis carcinomatodes (Neelson); sarcocarcinoma (Boehme), alveolar endothelial sarcoma (Podak), endothelioma (Eppinger and many others), carcinoma (Lepine, Benda, Dreesen, Ribbert, Orth, Sprunt, and Bayne-Jones). Bayne-Jones,[3] in 1919, in reviewing this controversy, aptly states that "this confusing terminology indicates that in the minds of the describers of the tumor there have been two uncertainties. These questions were: (1) What is the origin of the tumor? From the lining cells of the pleura or from the intima of the lymphatics? (2) What is the nature of the cells lining the pleura?"

Benda [4] and Sprunt [5] found areas in their sections in which transitions from the flat cells of the pleural lining to the villous and tubular arrangements of the large cells of the tumor could be seen. These

* From the Departments of Medicine and Pathology of the University of California Medical School.

1. Wagner: Arch. d. Heilk., 1870 and 1874, p. 634.
2. Schultz, R.: Endothelcarcinom, Arch. d. Heilk. **17**:1, 1876.
3. Bayne-Jones, S.: Carcinoma of Pleura with Hypertrophic Osteo-Arthopathy, Johns Hopkins Hosp. Rep. **18**:213, 1919.
4. Benda, C.: Ueber das primäre carcinom der pleura, Deutsch. med. Wchnschr. **23**:324, 1897.
5. Sprunt, T. P.: Primary Carcinoma of Pleura, Johns Hopkins Hosp. Bull. **22**:289, 1911.

observations suggest that their tumors arose from the lining cells of the pleura. The present view of most histologists is that the lining cells of the pleura are epithelial-like cells derived from the mesoderm when this layer splits to form the pleural cavity. If this is the case those pleural tumors which can be shown to be derived from the lining cells of the pleura may be regarded as epithelial tumors, or carcinomata. The chief difficulty in such determinations is, as Ribbert points out, that examination is never possible in the early stage of the process and must be made when the growth is far advanced and the whole pleura is involved. Adami [6] introduced a new terminology for these tumors. He designated them as mesotheliomas originating from the mesothelial lining of the serous cavity, which in turn, is derived from the mesoderm.

Adler,[7] in his splendid monograph on the primary malignant growths of the lungs and bronchi, takes the stand of Klaatsch [8] and is opposed to an ironclad classification of tumors based on their embryologic relations to the three germinal layers. He believes that embryology is tending more and more toward giving up the mesoderm as a primary germinal layer and is depending more and more on the entoderm and the ectoderm, with only secondary and varying assistance from a secondary mesoderm. He emphasizes the fact that functionally and physiologically endothelium appears closely related to typical epithelium. He agrees with Borst that there are tumors undoubtedly taking origin from endothelium, and, as the endothelium occupies a peculiar position, on the one hand, appropriating to itself some of the functions of epithelium, and on the other hand, being intimately associated with connective tissue, even forming fibroplastic cells, it is best to call these tumors by the special name endotheliomas. Adler states that he has never been convinced of the occurrence of primary malignant endothelioma in the lung itself, but he thinks such tumors undoubtedly do occur in the pleura.

The majority of observers, however, have followed Schultz and Eppinger and regard the origin of these neoplasms as being from the endothelial lining of the pleural lymphatics.

It is well known that vascular metastases are uncommon. Invasion occurs by direct extension through the lymphatics into the lung, pericardium, diaphragm, peritoneum and omentum, and implantation metastases are found frequently on the surface of the organs lying

6. Adami, J. G.: Principles of Pathology **1**:812, Philadelphia, Lea & Febiger, 1908.

7. Adler, I.: Primary Malignant Growths of Lungs and Bronchi, New York, Longmans, Green & Co., 1912.

8. Klaatsch, H.: Ueber den jetzigen Stand der Keimblattfrage mit Rücksicht auf die Pathologie, München. med. Wchnschr. **46**:169, 1899.

in the cavities into which the tumor has penetrated. This peculiar manner of extension suggested the possibility of an inflammatory nature of the process to some observers (Neelson, Perls, Fraenkel, Birch-Hirshfeld) and led Schweninger [9] in 1878 to designate the condition, "lymphangitis proliferans."

CLASSIFICATION OF PLEURAL TUMORS

Pallasse and Roubier [10] adopt the classification of all pleural tumors advocated by Guyot and Parcelier which is as follows:

(1) BENIGN GROWTHS: The benign tumors include the usual neoplasms which occur in other tissues, such as lipomas, chondromas and fibromas.

(2) MIXED GROWTHS: Several of these are described: for example, the chondrosarcoma (Ribbert). These neoplasms originate as benign tumors but tend to develop malignant characteristics.

(3) MALIGNANT GROWTHS PROPER: These are classified by M. Mentrier (in Traité de méd. Brouardel-Gilbert) and subsequently by Bloch [11] in his excellent monograph on this whole subject into two large subgroups, (a) sarcomas and (b) endotheliomas, these latter outnumbering the sarcomas about four to one. (From what has been said before, the propriety of the term endothelioma can be judged.)

The case which aroused our interest in this subject occurred on the medical service of Dr. Herbert C. Moffitt in the University of California Hospital during the past winter. We wish to take this opportunity to express our thanks to Dr. Moffitt for the privilege of studying this case, and to Dr. Glanville Y. Rusk, associate professor of pathology in the University of California Medical School, for many helpful suggestions in the preparation of this study.

HISTORY OF CASE

Dr. R. C., a physician, 40 years of age, American, native of California, was admitted to the medical service of the University of California Hospital, Feb. 19, 1920. He died March 22, 1920. Patient was first under the care of Dr. George H. Evans at St. Luke's Hospital and the following notes were obtained from the history of that hospital. Patient was first seen Sept. 22, 1919, and gave the following history:

Complaint.—"Shortness of breath," and "pain in the left chest."

Family History.—Unimportant.

Past History.—In November, 1918, he had a rather mild attack of influenza which was followed by slight dyspnea. In May, 1919, he first noticed pain in

9. Schweninger: Ann. d. Krankh. z. München., 1878, p. 365.

10. Pallasse, E., and Roubier, C.: Les Tumeurs primitives de la Plèure, Ann. de méd., Par. **111**:243, 1915.

11. Bloch, M.: Néoplasms malins primitifs de la Plèure (Thésé de Par.), (Paris, Vigot freres), 1905, No. 414.

the left chest, and at the same time he began to lose weight and feel below par. June 11, 1919, he had his tonsils removed and the immediate effect of this seemed to be good as he gained weight and strength afterward. However, the pain in the chest continued and the dyspnea increased. In August, 1919, a diagnosis of pleurisy with effusion (left) was made, and the patient had a thoracentesis with the result of the removal of more than a liter of bloody

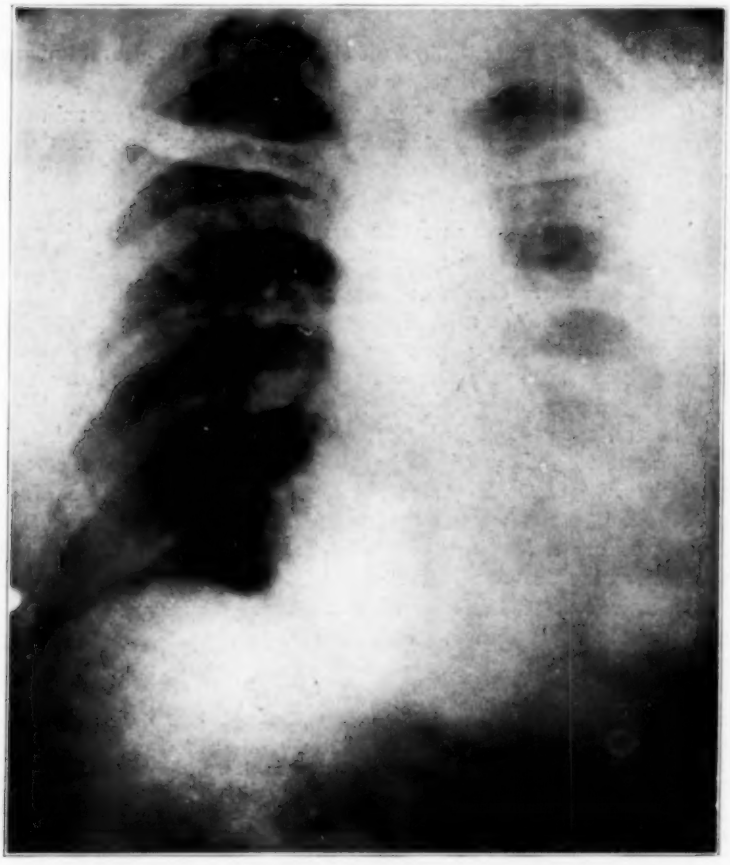

Fig. 1.—Roentgenogram (No. 14227, St. Luke's Hospital, Roentgen-Ray Department, Sept. 23, 1919) taken with the patient in the upright position.

fluid. Three days later thoracentesis was again performed and 28 ounces of bloody fluid was withdrawn. Sept. 22, 1919, the patient entered St. Luke's Hospital.

Physical Examination. — Nourishment fair. Pupils are unequal, the right pupil is larger than the left. The chest is asymmetrical; the left chest is flat and the left shoulder droops.

Roentgenoscopy of Chest: (Sept. 23, 1919.) The roentgenogram (Fig. 1) showed a grayness throughout the upper half of the left chest with a dense shadow at the left base which partially obscured the heart and diaphragm, although the heart was not displaced to the right. Interpretation of the plate left a doubt regarding the presence of fluid in the left pleura; while there was marked dulness at the left base, vocal fremitus and resonance were not entirely absent and no Grocco's triangle was present on the right side.

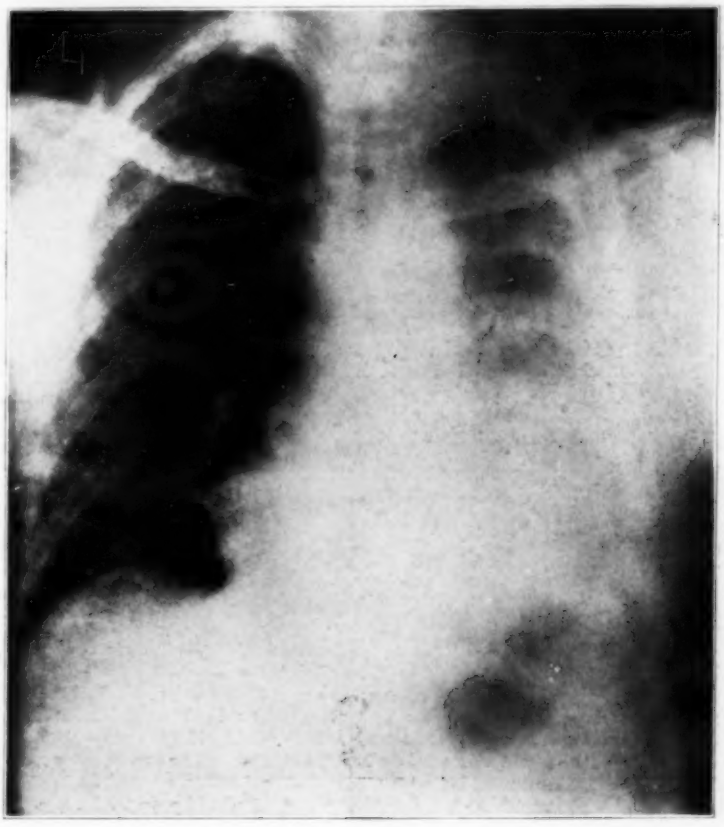

Fig. 2.—Roentgenogram (No. 14793, St. Luke's Hospital Roentgen-Ray Department, Dec. 30, 1919) taken with the patient in the upright position.

Blood examination: Hemoglobin, 95 per cent.; erythrocytes, 4,550,000; leukocytes, 8,000; polymorphonuclears, 72 per cent.; large lymphocytes, 28 per cent.; transitionals, 1 per cent.

Urine examination: entirely negative.

Patient continued to have considerable pain in the left lower chest. At this time he was afebrile, except following roentgen-ray exposure.

Oct. 8, 1919, the patient was allowed to return to his home at Hollister, Calif. He was forced to remain in bed after his return home and opiates were needed to relieve the pain in the left chest. About December 1, he was able to be up a few hours each day.

December 16, the patient was readmitted to St. Luke's Hospital.

Fig. 3.—Roentgenogram (No. 18161, University of California Hospital, Roentgen-Ray Department, March 6, 1920) taken with the patient in the prone position (anterior-posterior view).

Roentgenoscopy of Chest (Dec. 30, 1919): The roentgenogram (Fig. 2) shows great retraction of the chest on the left with what was apparently a thickened pleura at the left base.

The chest was tapped several times by Dr. Evans and bloody fluid was removed.

Jan. 24, 1920: At this time the patient began having periods when he was irrational. These periods increased until January 27 when he became very irrational, pulse rapid and weak.

March 2: The patient was transferred to the University of California Hospital.

Dr. Kerr's notes on admission: Thin, emaciated middle aged man, lying propped up in bed, face drawn, evidently in constant pain. The pain is periodical, located in the left chest and the left upper abdomen.

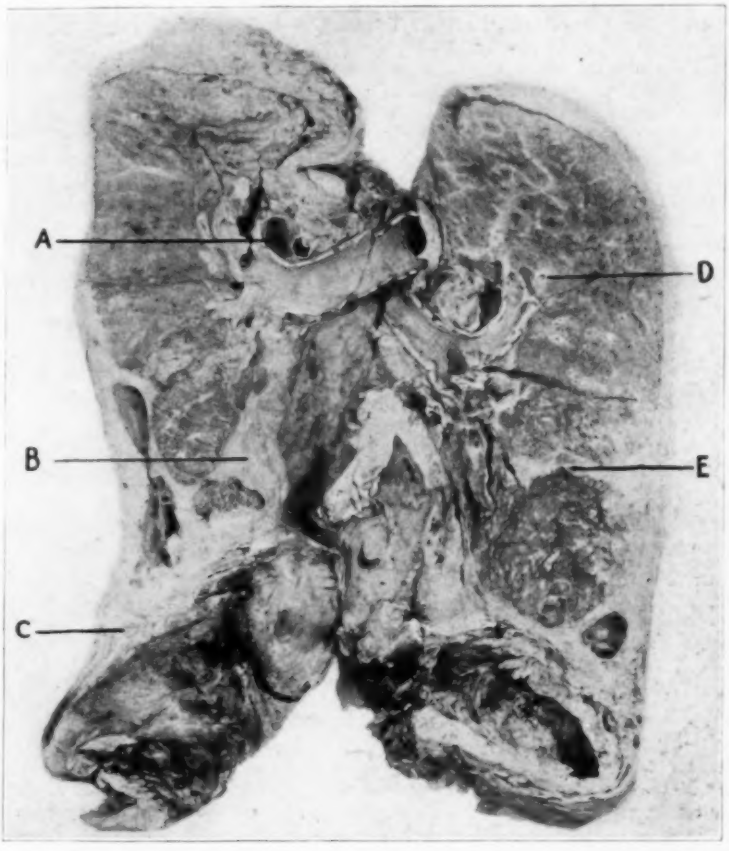

Fig. 4.—Photograph of cut surface of left lung showing the sheetlike thickening of the pleura, the enlarged glands at the hilus (a); thickening of pleura on mediastinal surface (b); remnants of diaphragmatic muscle (c); peribronchial tumor invasion (d); invasion of lung parenchyma by pleural tumor (e).

Pupils: Right is larger than the left; both are regular, and dilated, and react slightly. Fundi, negative

Chest: The left side of the chest is flattened and retracted. Excursion of the diaphragm is absent on the left, but present on the right. The percussion note over the right side is hyperresonant; it is flat on the left side from the

fifth rib in front downward, and from the angle of the scapula downward to the base on this side. Above this area of flatness in the left front there is an area of wooden tympany from the fourth rib upward to the clavicle. The breath sounds are bronchial in type in the upper part of the chest and distant to absent below, both anteriorly and posteriorly. No râles could be made out. No friction rub is palpable.

Heart: The right border is possibly displaced slightly to the left. The heart action is regular and rapid. The heart sounds are of poor quality. The pulses are equal, regular and of good volume.

Extremities: There is marked clubbing of the fingers. The left arm is definitely smaller than the right. Reflexes are equal on two sides and hyperactive throughout.

Sputum Examination: The sputum is very tenacious and of light lemon yellow. No odor or sulphur granules present. Preparation of fresh specimen shows great numbers of pus cells and many large phagocytic endothelial cells containing yellowish pigment. No Charcot-Leyden crystals or Curschmann's spirals were found. Stained specimens showed no bacteria, some cellular detritis with many pus cells and endothelial cells. No acid fast bacilli found.

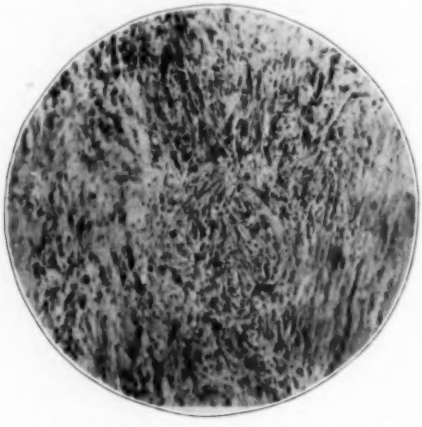

Fig. 5.—Section of the pleural tumor showing the diffuse type of growth (Objective 2, Ocular 4).

March 6: Patient complains of cramplike pains in the upper abdomen. The left abdominal wall is held rigidly. No masses can be made out by palpation or percussion.

March 8: Stool examination on five consecutive days has been negative.

Urine examination: negative, except for slight trace of albumin.

Roentgenoscopy of Chest (March 6, 1920): "The plates (Fig. 3) look quite different now than the plates (Figs. 1 and 2) made at St. Luke's Hospital. The former plates I interpreted as pointing to an effusion with thickened pleura on the left, and although I looked carefully for evidence of malignancy in the neighborhood of the hilus, I was never sure that such a condition was present. Now it seems that one plate indicates quite definitely that a malignant process is present with a mass at the left hilus and displacement of the mediastinum toward the affected side." (Dr. Ruggles.)

March 9: Patient had diarrhea during the past week and today has some abdominal pain with some abdominal muscle spasm and distention.

March 10: Patient is drowsy. There has been an abrupt rise in temperature, pulse and respiration. During the past two days the patient had two roentgen-ray exposures of the chest, but these were very short exposures and probably of no marked therapeutic value.

March 12: Temperature, pulse and respiration continue elevated. There is a small area of dulness with bronchial breathing at the right base. Diarrhea continues.

March 13: Patient slightly better today.

Blood Examination: Erythrocytes, within normal limits; leukocytes, 17,600; polymorphonuclears, 82 per cent.; small lymphocytes, 6 per cent.; large lymphocytes, 8 percent.; endothelial cells, 2 per cent.; eosinophils, 1 per cent.; transitionals, 1 per cent.

Rectal Examination, March 16: High up and transversely situated, there is a firm, painless mass. The abdomen is held rigidly and an elongated, tender mass, 6 by 2 cm., can be palpated parallel to the descending colon at the brim of the pelvis.

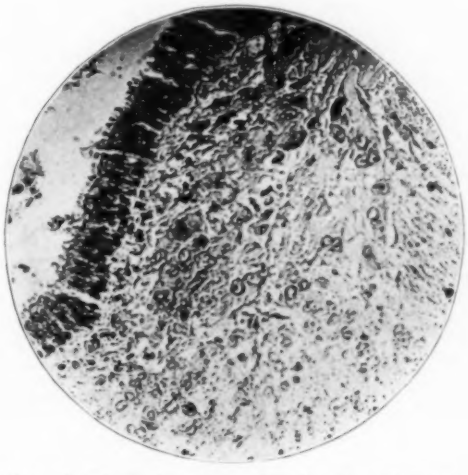

Fig. 6.—Section of a large bronchus, showing the extension of the growth along the submucosa (Objective 9, Ocular 4).

March 17: Condition practically unchanged.

March 18: Blood cultures: no growth in twenty-four hours, forty-eight hours, or six days.

March 22: Patient sank rapidly the last three or four days and died today.

Diagnosis: Final impression (recorded before postmortem).—Tumor of the left pleura with extension into the left lung and peritoneal cavity.

ABSTRACT OF NECROPSY (A. 20.50)

Anatomic Diagnosis: Primary tumor of the pleura, filling the left pleural cavity, invading the left lung and pericardium, and extending through the diaphragm with extensive invasion of omentum and multiple implantations over the peritoneum, also superficial invasion of spleen and liver. Multiple peritoneal adhesions with fibrinous plaques, associated with the adhesions in the pelvis. Adhesions of thickened omentum in left pelvis. Cloudy peritoneal

exudate. Marked atelectasis and edema of left lung. Moderate compensatory emphysema of right lung. Deformity of left chest. Misplacement of rectum (apparently congenital) to the left.

The body is that of an emaciated male adult of good stature. Rigor mortis is absent. Bodily heat is well retained. The left chest is diffusely sunken and the skin shows a blotchy hyperemia. At the usual site there is a well healed scar of an appendix operation. The pupils are circular, equal and moderately dilated. The sclerae are negative. The ears are negative. The fingers show moderate clubbing. The extremities are otherwise negative.

On making the usual median incision, the bodily fats are found to be deficient. The peritoneal cavity contains about 500 c.c. of turbid fluid which is without color. The omentum is greatly thickened, especially along its lower edge. It is drawn upward on the right side, but on the left side it is adherent by readily separable subacute adhesions to the cavity of the false pelvis and to the top of the bladder. The peritoneal cavity generally shows

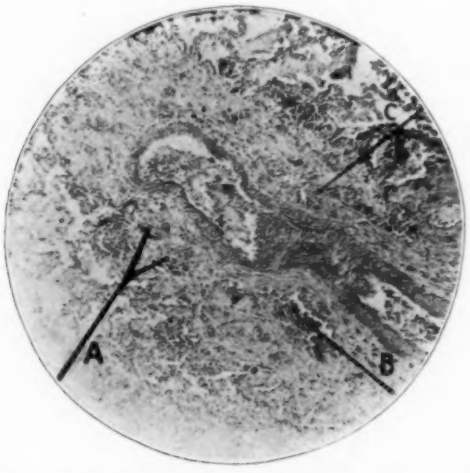

Fig. 7.—Section of lung parenchyma including a small vein showing the extension of the growth along the perivascular lymphatics (a, b and c) (Objective 3, Ocular 4).

a number of subacute readily separable adhesions on the upper and lower surface of the liver, in the convexity of the spleen, between the loops of small intestine and on the mesentery, also around the head of the cecum. In the pelvis the rectum is displaced to the left of the midline, and while there are adhesions about it they do not seem dense enough to have pulled the rectum over but it appears to be a congenital anomaly. At the site of the adhesions, especially those of the omentum where it is adherent to the bladder and on the surface of the loops of small intestine in the pelvis, there are a number of fibrinous flakes but unassociated with any hyperemia. The edge of the omentum is greatly thickened by an invading white, semitranslucent, cellular looking material, forming a cakelike mass, about 2 cm. thick by 5 cm. broad, near its adhesions in the left pelvis and becoming somewhat thinner as it extends upward across the abdomen. In the main mass of the omentum one sees similar implantations. The mesentery and peritoneal surfaces of the intestine show a number of tiny white implantations, some of

which are fairly well circumscribed and surrounded by a zone of hyperemia but others fade off at the edges and even show a tendency to infiltrate the surrounding tissue, and occasionally there is a slight puckering in the immediately adjacent tissue. Similar implantations occur in the pelvis and to a less degree on the parietal peritoneum.

The costal cartilages are unusually calcified for an individual of his age. The posteriar surface of the sternum shows diffuse adhesions on the left; there are none on the right. The right pleural cavity is free from adhesions, the left is entirely obliterated by dense chronic adhesions, on separating which the intercostal muscles show streaks of white fibrosis. The pericardial cavity shows a few readily separable subacute adhesions between the left side of the heart and the parietal pericardium over an area about 3 by 4 cm. The cavity also contains about 20 c.c. of serous transudate.

The heart is of normal size. The left ventricle is adherent, as noted above, to a somewhat roughened opaque area on the parietal pericardium, apparently due to an invasion of new growth from the overlying adherent pleura. The

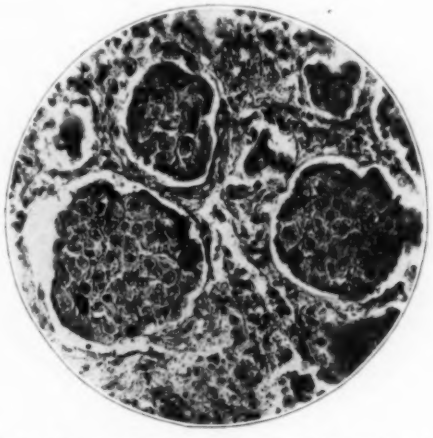

Fig. 8.—Section of lung parenchyma showing the masses of tumor cells to the alveolar spaces. Note the type of growth here (Objective 9, Ocular 4).

right side is somewhat full but not dilated. The endothelium of all the chambers including the valves is negative. The myocardium is of normal thickness, and slightly pale, but is otherwise negative. The first portion of the aorta shows a small amount of atheroma but is otherwise negative.

The right lung is moderately emphysematous, and shows the usual pigmentation. At the apex there is a slightly puckered scar surrounded by a narrow zone of parchment-like thickening of pleura. On section of the lower lobe there is a small calcified nodule about 2 mm. in diameter, apparently the remains of a tubercle. The lung is otherwise negative. The bronchi at the root are negative.

The left lung is removed with great difficulty on account of the universal dense adhesions. The organ appears to be about half its normal volume, and universally covered with a white fibrous layer which on section varies from about 2 to 5 mm. in thickness. Section through the lung shows the organ to be greatly compressed, and almost airless, except in the upper lobe. There is a moderate diffuse edema. The main bronchi were opened and no evidence of primary growth was seen. In the tissues just beneath the hilum and extend-

ing through to the pleura is an area which is relatively more firm, and contains a rather diffuse, though somewhat spotted, overgrowth of connective tissue. In this region as well as occasionally elsewhere in the lower lobe one sees a bronchus with definitely thickened walls due to a uniform white fibrous-looking tissue. The lymph nodes at the root show the usual pigmentation and some fibrous tissue invasion but nothing suggesting new growth. The thickened pleura likewise is so diffusely fibrous that one can make out no areas where the tissue appears more cellular as if from new growth. In the lower lateral angle of the lung the thickened pleura is separated into two leaves forming an irregular small cavity which contains a number of septa and about 15 c.c. of a clear straw-colored fluid.

The diaphragm on the left side was removed with the lung. It is composed of an opaque white tissue appearing somewhat more cellular than the pleura generally, also somewhat softer. Its under surface is greatly roughened and shaggy, and the spleen is adherent to it. On separating the latter there

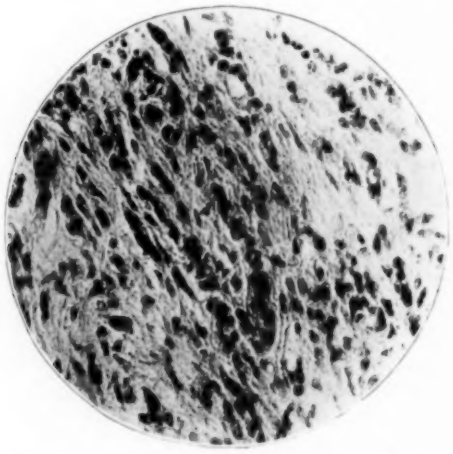

Fig. 9.—Section of omental tumor showing the diffuse type of growth (Objective 9, Ocular 4).

is noted an irregularly outlined layer of white semitranslucent material, apparently adherent new growth invading through the diaphragm.

The spleen is slightly reduced in size. On section it appears soft, and rather dark as if containing considerable blood. The malpighian bodies are small and indistinct and there is a moderate grade of fibrosis. At one point there is a deeply running scar about 1 cm. long by 2 cm. broad, connecting with the overlying new growth. This, however, somewhat resembles an old infarct.

The liver is slightly undersized. Superficially it shows a number of scattered, depressed, slightly scarred white areas which on section run a variable distance into the substance of the liver. The larger ones invade the liver parenchyma for a distance of 1.5 cm. Some of these are composed of fibrous tissue, others show areas suggesting necrosis and still others are markedly calcified. About each of these is a small amount of fibrosis. The gallbladder is deeply set in the liver. It appears negative, however, on section. The liver parenchyma shows a slightly mottled appearance due to a slight grade of passive congestion.

The suprarenals appear normal.

The kidneys are of normal size. The capsules strip normally. The fetal lobulations are slightly persistent. The surface is pale. On section the cortex is of normal thickness, and well differentiated from the medulla. The former is pale. The anatomical markings are regular. The kidneys are otherwise normal.

The pancreas is of normal size and negative on section.

The mesenteric and retroperitoneal lymph nodes are negative.

The mucosa of the gastro-intestinal tract is negative.

The aorta is normal.

The bladder, prostate, seminal vesicles and testes appear normal.

Microscopic Notes: *Pleural Tumor.*—The pleural surface is covered by a thickened sheetlike mass composed of a dense hyalin, rather acellular, connective tissue. All vestiges of the mesothelium of the two pleural surfaces have been obliterated. Along the costal margin of the thickened pleura there

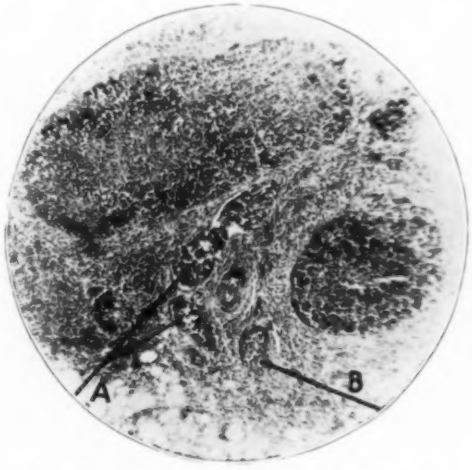

Fig. 10.—Section of mesenteric lymphoid nodule showing extension of tumor along the lymphatics (a and b) (Objective 3, Ocular 4).

is a rather diffuse distribution of tumor cells. Except in certain areas these cells are limited to a narrow zone along the surface. At certain points these cells extend more deeply into the thickened pleura, but at no point in the numerous sections examined do they become continuous with the nests of tumor cells along the inner zone of the thickened pleura adjacent to the lung. The morphology of the cells and the structure of the tumor are variable. The greater portion of the tumor shows a rather marked desmoplastic reaction with the tumor cells distributed rather diffusely throughout the fibrous tissue. In this diffuse type of growth the cells are elongated, have a homogenous acidophilic cytoplasm with an oval or elongated, hyperchromatic, moderately vesicular nucleus with one or more small faintly staining nucleoli. There are also numerous elongated multinucleated syncytial protoplasmic masses which show no intercellular differentiation. Mitotic figures are not numerous where the desmoplastic reaction is marked. There are also a few small nests of cells which occupy small lacunae in the connective tissue. None of these spaces have an endothelial lining. These cells resemble those described above, except

in general shape. They are spherical in shape, have a homogenous, deeply staining cytoplasm, with a round, hyperchromatic, moderately vesicular nucleus, with one or more small faintly staining nucleoli. Among these cell groups mitoses are more numerous. Along the inner zone of the thickened pleura adjacent to the lung parenchyma, the tumor cells occur in groups at intervals, but do not have the general distribution as noted along the costal margin. The variations in structure of the growth are the same. Many of the subpleural lymphatics are filled with tumor cells. These cells appear to have no relation to the endothelial cells lining the lymphatics. At many points the alveoli of the subpleural lung parenchyma are filled with masses of tumor cells, also an occasional small vein shows invasion. These cells are similar in every respect to those of the cell nests along the costal margin.

Lymph Glands of Hilus.—Sections of two enlarged lymph glands at the hilus of the lung show a rather diffuse tumor invasion. Many of the lymph spaces are distended with tumor cells. There are also large areas of diffuse tumor invasion with marked fibrosis.

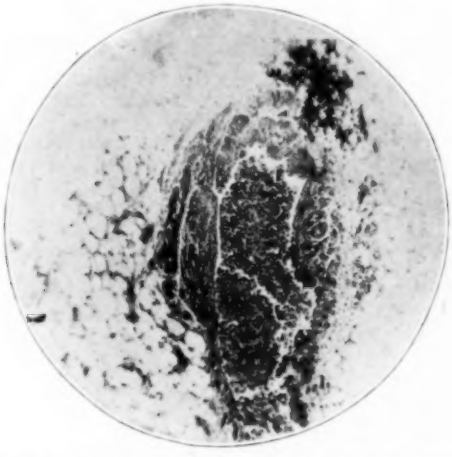

Fig. 11.—Same section as Figure 7, showing direct invasion of an adjacent vein (Objective 3, Ocular 4).

Bronchi.—Numerous sections taken from various portions of the bronchi show no evidence of involvement of the epithelium of the mucosa. Most of the bronchi show an extension of the tumor cells along the lymphatics of the submucosa. In some instances the cells extend along the finer lymphatics, approaching the epithelial lining of the mucosa. In some areas along the submucosa there is a marked desmoplastic reaction resulting in great thickening of the submucosa. There are also areas in which this desmoplastic type of growth has extended into the peribronchial tissues. There are numerous extensions of tumor cells into the alveolar spaces of the adjacent lung parenchyma.

Lung Parenchyma.—The subpleural lung parenchyma shows a compression atelectasis. The deeper lung parenchyma shows alternating areas of atelectasis and emphysema with a rather diffuse edema. There are several large areas of coagulative necrosis. In these areas the outlines of the alveolar spaces persist and are packed with large mononuclear polygonal cells. These areas represent areas of tumor invasion with necrosis. There are a few small foci of liquefaction in the areas of necrosis with an accumulation of poly-

morphonuclear leukocytes. In some areas the alveoli contain masses of fibrin but no cellular exudate. There is an occasional small bronchus which is filled with an exudate of polymorphonuclear leukocytes. Many of the lymphatics of the bronchioles and surrounding the blood vessels are distended with tumor cells. From these there are extensions of tumor cells into the adjacent alveolar spaces.

Diaphragmatic Surface of Pleura.—The tumor has invaded the diaphragm by direct extension, this extension being aided by invasion and extension along the lymphatic spaces. There are a number of lymph spaces which are distended with tumor cells. The growth here shows a marked desmoplastic reaction. In some of the sections the diaphragm persists as a few hyalinized fragments of skeletal muscle distributed throughout the growth.

Omental Tumor.—The omental nodules are similar in structure to the pleural growth. The growth here shows an active connective tissue reaction with tumor cells distributed diffusely throughout. The connective tissue stroma is

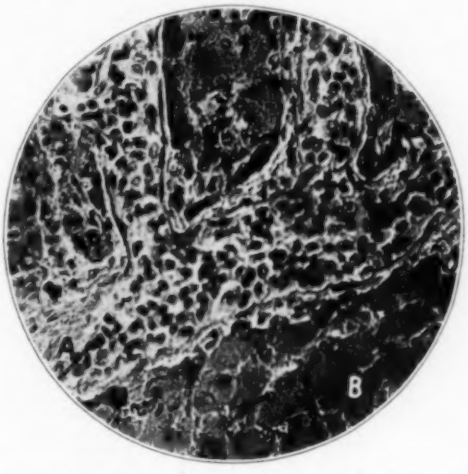

Fig. 12.—Section of liver showing the extension of tumor cells along the lymphatic (a); liver cells (b); (Objective 9, Ocular 4).

relatively less abundant and more cellular than in the pleural growth. There are numerous lymphatic spaces which are filled with tumor cells. Mitotic figures are also more numerous than in the pleural growth. The tumor cells present the same variation in morphology as elsewhere.

Mesenteric Lymph Nodes.—The lymph nodes in some instances are practically replaced by tumor cells. Many of the lymphatic spaces are distended with tumor cells. Some of the adjacent small veins show a direct invasion. The peritoneal implantations are small and superficial and do not invade the musculature of the intestine.

Spleen.—The spleen shows a marked diffuse passive congestion. The malpighian bodies are small and widely separated. At one point on the surface is a flat tumor mass, similar in structure to the omental tumor. At another point there is a bandlike projection of fibrous tissue into the splenic pulp. Through this dense fibrous stroma there are numerous tumor cells. An occasional mitotic figure is seen.

Liver.—There are numerous depressed areas on the surface of the liver. From these depressed areas there are bandlike projections into the liver parenchyma. These are composed of neoplastic tissue, similar to the omental growth, except that they are more scirrhus in type. At numerous points not far removed from the larger areas of tumor growth the interlobular lymphatics and veins are plugged with tumor cells. The adjacent liver lobules show no invasion. In the large tumor masses there are areas of hyalinization with calcification.

The remainder of the viscera show no evidence of metastases nor anything of importance in relation to this case.

Summary of Microscopic Picture.—The cell type and manner of growth is variable, apparently dependent on surrounding environment. In those locations where the growth is apparently not hampered, the cells are of medium size, spherical in shape, have a homogenous eosinophilic cytoplasm, a relatively large round or oval, hyperchromatic, moderately vesicular nucleus, with small faintly staining nucleolus. This type of cell is found in the lymph nodes, lung parenchyma, and the extensions along the lymphatics. In these locations the cells tend to group together and assume a form of growth similar to epithelial growths. In those locations where the desmoplastic reaction is marked, the cells do not tend to group together but are diffusely disseminated throughout the connective tissue. The cell type in these areas is variable. There are numerous isolated cells similar to those described above. There are also numerous elongated or fusiform cells. These vary from those described above only in shape, the intracellular characteristics being the same. Some of these cells roughly resemble the young fibroblasts; however, they can be easily differentiated by their more chromatic nuclei and dense eosinophilic cytoplasm. There are also elongated multinucleated cytoplasmic masses which show no intercellular differentiation. It is evident that all of these cells are the same, with variations in shape and grouping, dependent on the surrounding environment of growth. It is also evident that the natural tendencies of these cells are to grow in an alveolar or medullary form. This is evidenced by the relatively larger number of mitotic figures in these areas.

Point of Origin and Mode of Extension.—In this case the growth is so far advanced that it is impossible to determine definitely the point of origin of the tumor, as the mesothelium of both the visceral and parietal pleura has been completely obliterated. Since the tumor cells are distributed rather diffusely over the costal surface of the thickened pleura and are separated from the inner zone adjacent to the lung by a layer of dense connective tissue, in which there are no tumor cells; and, furthermore, since the tumor cells occur only at widely separated intervals along the inner zone, one is influenced in drawing the conclusion that: the tumor probably arose at some point on the parietal pleura and extended secondarily to the visceral pleural surface, probably being favored by the inflammatory adhesions. Since the tumor does not possess the general characteristics of the endotheliomas derived from lymphatics and blood vessels, and is quite analogous in many respects to those tumors whose etiology has been traced to the lining mesothelium of the pleura (Benda [4] and Sprunt [5]), we feel justified in concluding that this tumor arose from the mesothelial lining of the pleura.

The mode of extension of the tumor is by continuity over contiguous surfaces, also by invasion and growth along the lymphatics. There are a few instances of direct invasion of the veins, but there is no evidence of a blood metastasis. The principal invasion of the lung is from the hilus along the bronchial and perivascular lymphatics. The invasion of the diaphragm is by direct extension, incidently invading and growing along the lymphatics.

Microscopical Diagnosis.—Although the mesothelial cells of the pleura have many of the characteristics of epithelial cells we do not see the justification of calling these tumors carcinomas. Likewise, since the mesothelial cells of

the pleura are usually regarded as being histologically and embryologically distinct from endothelial cells of the subpleural lymphatics and blood vessels, the term endotheliomas is not appropriate. We prefer to designate the tumor as a primary mesothelioma of the pleura.

OCCURRENCE

Glockner,[12] in 1897, collected forty-two primary malignant pleural tumors and added seven of his own. Bloch, in 1905, collected forty-seven cases of endothelioma and sixteen of sarcoma. Patterson [13] reported two of his own cases and collected ninety-six others; however, some of these could not be considered authentic because the data in regard to them was incomplete. The disease occurs more than twice as frequently in men than in women, and the greatest number of cases are found between the ages of 40 and 60. It appears to be a little more common on the right side than on the left, although it may be bilateral.

SYMPTOMS AND COURSE

The onset of pleural malignancy is usually insidious, and the course, once initiated, is progressive. Occasionally, the onset may be stormy with rapid development of the typical symptoms of an acute pleurisy. In the usual course the patient will be able to follow his business for some time, but he finds that he is losing energy, tires easily, and becomes dyspneic readily on the least exertion. Following this a dull, heavy, indefinite pain is noted in the chest. As a rule, there is little cough or expectoration, and the patient remains afebrile. Usually by the time the patient enters the hospital asthenia and cachexia are striking features. Paroxysmal attacks of dyspnea may occur and a state of "pseudoasphyxique generalement" (Bloch) becomes pronounced. The whole picture at this time strikes one as an advanced phthisis or myocardial disease in the terminal stage. The average duration of the disease from the onset of symptoms is from six to nine months.

PHYSICAL SIGNS

Immobilization, flattening and finally retraction of the affected side are the salient findings on inspection in pleural malignancy. Palpation may reveal enlarged glands in the neck or axillae, but they are not constant. The percussion signs indicate pleural effusion or thickened pleura which are not altered by pleural puncture and the removal of large amounts of fluid. The auscultatory findings point to the presence

12. Glockner, A.: Ueber den sogenannten Endothelkrebs der serosen Haute (Wagner-Schultz), Ztschr. f. Heilk. **18**:209, 1897.

13. Pattersen, H. S.: A Case of Endothelioma of the Pleura with a Review of Ninety-Six Cases, J. M. Soc. New Jersey **5**:373 (Jan.) 1909.

of a pleural exudate. In general there is nothing pathognomonic in the physical signs of this disease. The signs may vary as with the different types of pleurisy of other origins, depending on the amount of fluid present, the duration of its presence and finally the amount of thickening of the pleura. Nevertheless, fluid is present in some stage of the disease in practically every case (Bloch), and it is usually of the hemorrhagic type. It is notable that in some instances the first puncture will show a serous fluid which subsequently will become hemorrhagic or purulent. The amount of fluid is abundant and reforms rapidly after withdrawal. One of the most significant observations is relative to the temperature, which usually remains normal throughout the entire course of the disease. Exceptionally, there may be an evening elevation but this is usually found to be due to a superimposed pulmonary infection. Direct infection of the pleural fluid also occasions a rise in the temperature in certain instances. Accompanying the usual afebrile state the pulse likewise remains normal.

DIAGNOSIS

With all the refinements and possibilities of our modern diagnostic methods, primary neoplasm of the pleura cannot be diagnosed clinically with absolute certainty in all cases, although its presence can strongly be surmised in a fair proportion. It must be remembered that our clinical impressions, supplemented with the most careful laboratory methods, may indicate a neoplasm of the pleura only to find at necropsy that the primary growth is in the lung or elsewhere in the body.

The factors of most importance in the clinical diagnosis of this disease are composite rather than simple, and should, in the first place, take into consideration the symptoms and the special observations mentioned in regard to the history and physical signs; in other words, the clinical picture as a whole, as presented by the patient, is of great value. An individual with the signs of pleurisy with effusion in whom there is discovered a dark colored, hemorrhagic, pleural fluid (at times chocolate-like) which tends to increase rapidly after withdrawal and to become more hemorrhagic on subsequent withdrawal, should be regarded with suspicion as harboring an intrathoracic neoplasm. Add to this that symptomatically the withdrawal of the fluid affords little or no relief and at times increases the pleural pain, and that the physical signs are but slightly altered, if at all, by the drainage of the pleural cavity and other evidence of malignant intrathoracic disease is present.

The retraction of the chest wall, with obliteration of the intercostal spaces and the increased resistance met by the trocar in passing through

the pleura in performing the thoracentesis, are observations of some value, although not pathognomonic of pleural new growth since they may be noted also in tuberculous adhesive pleurisy. Small nodular implantation growths along the tract of the trocar puncture following thoracentesis have in rare instances afforded material for microscopic examination, as have fragments of tissue found on the point of the trocar on its removal. In doubtful cases which have baffled all the ordinary procedures and the diagnosis remains obscure, exploratory thoracotomy is helpful and justifiable. This procedure was done in Bayne-Jones' case.

ROENTGEN-RAY DIAGNOSIS

Unfortunately, the roentgen ray affords little help in determining the exact nature of the pleural disease in these cases. Barjon,[14] in his recent monograph on radiodiagnosis of pleuro-pulmonary affections, says: "Cancer of the pleura offers little of interest from the radiological point of view. It is seen most often under the form of pleurisy of the large cavity with effusion. Radioscopically it does not differ from ordinary pleurisy and it is for the clinician alone to prove its nature." Manges,[15] in a recent paper, confirms this statement and says that in his opinion pleural tumors in nearly all instances have massive effusions which constitute the only roentgen-ray findings.

CYTODIAGNOSIS

It is to Widal and Ravaut [16] that the credit of having first shown the importance of a careful histologic examination of the cell contents of pathologic effusions is due. As the result of their investigations, they stated their so-called cytologic formulae, which, in general, hold good in the majority of cases. Briefly, they are:

1. An excess of lymphocytes indicates a tuberculous process.

2. A preponderance of polymorphonuclear cells indicates an acute inflammatory process, frequently due to a pneumococcal or a streptococcus infection.

3. A passive or mechanical transudation contains, as a rule, a large number of endothelial cells, which often occur in groups ("placards"). (Besides the cardiac and renal transudates, malignant pulmonary and pleural disease are included in this group and present the same cytologic picture.)

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14. Barjon, F.: Radiodiagnosis of Pleuropulmonary Affections, New Haven, Yale University Press, 1918. (Translated by J. A. Honeij.)

15. Manges, M.: The Roentgen Ray in the Diagnosis of Pneumonia, Pleural Diseases and Pulmonary Tumors, New York M. J. **106**:917 (Nov. 17) 1917.

16. Widal, F., and Ravaut, P.: Compt. rend. Soc. de Biol. **52**:648, 1900.

It is the experience of numerous observers that in many cancerous pleurisies cancer cells are not found in the transudate, but in others they are present, and if identified seem to clinch the diagnosis. The recognition of cells of the different neoplasms is often very difficult, because some resemble lymphocytes, and others endothelial cells. Warthin [17] diagnosed sarcoma of the pleura by means of numerous spindle cells found in the pleural fluid obtained by aspiration and there are a few similar examples in the literature. It is of some importance to find cells in active mitosis in effusions. Warren,[18] in a study of the diagnostic value of mitotic figures in the cells of serous exudates, concludes that the presence of numerous cells undergoing mitotic division in serous exudates are almost diagnostic of malignant disease. These mitoses are more common in sarcoma than in carcinoma, the presence of a small number are of no significance, and in the majority of the effusions associated with malignant disease no division figures are seen in the cells.

Undoubtedly the early work in cytologic studies inspired too much optimism as to its ultimate value in the diagnosis of puzzling cases. The method offers a means which will usually exclude some inflammatory condition complicating a neoplasm, for here polymorphonuclear cells may predominate to such an extent as to lead to the conclusion that some acute infectious process is present overshadowing the associated malignant disease. We must conclude that cytodiagnosis is of a very limited value in the clinical diagnosis of malignant pleural disease.

CHEMISTRY OF PLEURAL EFFUSIONS IN THE DIAGNOSIS OF MALIGNANCY

Chemical studies of pleural effusions have not yielded a practical method for determining whether or not an effusion in a serous cavity is of malignant origin. The specific gravity and albumin content are of little value. Morris [19] studied the incoagulable nitrogen of puncture fluids with especial reference to cancer, and he came to the conclusion that a serous effusion with incoagulable nitrogen below 0.07 gm. per cent. is probably not of malignant origin. This increase of incoagulable nitrogen in certain carcinomatous fluids was thought to be due to the presence of proteolytic enzymes. It remains for the chemistry of

17. Warthin, A. S.: The Diagnosis of Primary Sarcoma of the Pleura from Cells Found in the Pleuritic Exudate, Med. News **71**:489, 1897.

18. Warren, L. F.: The Diagnostic Value of Mitotic Figures in the Cells of Serous Exudates, Arch. Int. Med. **8**:648 (Nov.) 1911.

19. Morris, R. S.: The Incoagulable Nitrogen of Puncture Fluids, with Special Reference to Cancer, Arch. Int. Med. **8**:457 (Sept.) 1911.

the future to supply us with a reliable test for the presence of malignancy, and judging by the progress of the past it does not seem improbable that this will be developed.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis several conditions must be taken into consideration. The most difficult and important disease to exclude in establishing a diagnosis of primary malignancy of the pleura is pulmonary tuberculosis in one of its diverse forms, and this, in truth, may not be possible even after a most painstaking study. The clinical history, physical examination, roentgen-ray findings, and a complete study of the pleural fluid, including its cytology, bacteriology and chemistry, may leave one in doubt, and in such a case certainty in diagnosis can be obtained only by an exploratory thoracotomy. Needless to say, such a procedure should not be adopted hurriedly, but it has its place today among the recognized diagnostic methods in obscure intrathoracic disease in which the other methods have failed.

Fortunately, in the majority of cases, if our clinical sense is alert and laboratory methods are utilized wisely, a correct diagnosis can be established.

The type of tuberculosis which may simulate a pleural neoplasm most closely is that which involves the pleura and lung almost simultaneously and is accompanied by a hemorrhagic pleural effusion. Although this is not a particularly common type of pulmonary tuberculosis, nevertheless, it is the most frequent condition which causes hemorrhagic pleural fluid. Besides malignancy of the pleura, lung and mediastinum, the other well recognized causes of hemorrhagic effusions include, traumatic and postoperative hemothorax, simple or idiopathic hemothorax, and the hemothorax which occasionally occurs in the course of chronic nephritis or cardiac disease. These last mentioned conditions are far less difficult to exclude in establishing the diagnosis of pleural malignancy.

Besides the application of these special methods to exclude tuberculosis, sedimented specimens of the pleural effusion should be examined in stained smears and by inoculation tests. The best results have been obtained by the use of comparatively large amounts of sedimented puncture fluid (from 40 to 50 c.c.) injected intraperitoneally into a guinea-pig. Continued negative results by this method are strong corroborative evidence against the presence of tuberculosis.

Following the exclusion of pulmonary tuberculosis, the next most difficult condition to differentiate from primary pleural new-growth is neoplastic disease of the lung, either of the primary or of the metastatic type. In the presence of a hemorrhagic pleural fluid with tuberculosis

excluded, a new growth of the lung should be considered more seriously than malignant pleural disease because the former occurs with far greater frequency. The special points that may prove of some value in differentiating primary pulmonary neoplasm from pleural malignancy are: (1) the early and persistent irritating cough encountered frequently in primary pulmonary tumors; (2), the typical currant jelly sputum and frequent hemoptysis; (3) finding the Lenhartz cell (Adler) in the sputum; (4), the absence of pain in some cases when seen early before the pleura has been involved (whereas pain is the most constant and distressing symptom from the onset in primary pleural tumors); and (5), the positive evidence afforded by the roentgen-ray study of the pulmonary neoplasm. Respiratory difficulties, cachexia, secondary anemia, an afebrile course, anisocoria, difference in the two pulses, clubbed fingers and variations in the cytologic picture and the chemistry of the pleural transudate may occur in both diseases and consequently are of no distinct aid in determining the exact point of origin of the disease process.

It is a well recognized fact that the symptoms and course of secondary lung tumors is quite distinct from the symptoms and course of primary pulmonary tumors (Adler). Such atypical and suggestive clinical pictures in intrathoracic disease should put one on guard, and a thorough search for the primary growth elsewhere should be instituted.

SUMMARY

We consider the cardinal points made in this paper to be as follows:

1. Primary, malignant, pleural tumor is a very rare condition.

2. These tumors constitute a distinct group and present a rather constant pathologic picture.

3. The definite point of origin of these neoplasms has not been determined absolutely.

4. We favor the mesothelial origin, and prefer to designate the tumor as mesothelioma rather than carcinoma, notwithstanding the fact that most of these neoplasms have been reported under the term endothelioma.

5. In the case presented above, the clinical diagnosis of malignant pleural disease was substantiated by the necropsy findings.

6. Pain in the chest is the earliest and most significant single symptom. It is usually severe and persistent in character and presents the most distressing feature of the disease.

7. The clinical course is of comparatively short duration and is usually afebrile.

8. There is nothing pathognomonic in the physical signs of the disease. A persistent, rapidly re-accumulating, hemorrhagic, pleural fluid is suggestive, and in its presence the possibility of pleural new growth should always be kept in mind.

9. The clinical picture studied as a whole offers the most valuable and trustworthy evidence.

10. The roentgen-ray examination fails to determine the exact nature and site of origin of the disease process in pleural malignancy.

11. Cytodiagnosis and the chemical study of the pleural transudates are of very limited value.

12. In those instances in which an exhaustive study has failed to establish a diagnosis, and pleural malignant disease is suspected, an exploratory thoracotomy is justifiable.

13. The two most important and at the same time difficult diseases to exclude in the differential diagnosis are pulmonary tuberculosis with hemorrhagic pleural effusion and primary malignant disease of the lung or bronchus.

FAT METABOLISM IN DIABETES MELLITUS*

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In the chemical investigation of diabetes in the past, interest centered chiefly about the question of disturbed carbohydrate metabolism, especially its attendant manifestations of glycosuria and hyperglycemia. Although the fact that in diabetes there is an impaired metabolism of fats as well as carbohydrates has long been recognized, the study of this phase of the problem, by accurate chemical methods, was begun only a few years ago. A simple procedure for the determination of lipoids in human blood was described by Bloor,[1] Joslin,[2] Joslin, Gray and Bloor[3] and Gray,[4] who pointed out the significance of an increased concentration of fat in diabetic blood.[5] Quite recently Brigham[6] emphasized the importance of controlling hyperlipoidemia in the treatment of diabetes. He says, "until the fat concentration of the blood is reduced no progress in increasing a sugar tolerance can be made." Analytical data bearing on this point are still meager and it seems desirable to add our observations to those already recorded in the literature.

We have made an analytical study of the sugar, fat and cholesterol in the blood in thirty-four cases of diabetes, noting the relationship of these substances to each other and to the diet.

PLAN OF INVESTIGATION AND METHODS

The subjects were patients in the diabetic unit of the department for the study of nutritional diseases of the Clifton Springs sanitarium. They included individuals of both sexes, varying in age from 8 to 73 years, and were in various stages of the disease. Chemical examination of the blood was made soon after admission, and the Allen-Joslin dietetic treatment for diabetes was begun immediately. Specimens of blood were thereafter analyzed for sugar, total lipoids[7] and whole

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*From the Biochemical Laboratory and the Unit for the Study of Nutritional Diseases of the Clifton Springs Sanitarium.

1. Bloor, W. R.: J. Biol. Chem. **17**:377 1914; **26**:417, 1916.
2. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia and New York, 1917, p. 100.
3. Joslin, Bloor, Gray: J. A. M. A. **69**:375 (Aug. 4) 1917.
4. Gray, H.: Boston M. & S. J. **178**:16, 50, 91, 120, 156, 1918.
5. These authors also summarize the literature and give a bibliography of the most important publications on the subject.
6. Brigham, F. G.: Boston M. & S. J. **183**:166, 1920.
7. By total lipoids we mean glycerids, phosphatids and cholesterol, as defined by Bloor, and determined as fatty acids.

blood and plasma cholesterol at frequent intervals, as indicated by the therapeutic needs of the patient. Blood for analysis was taken before breakfast, and on a diet of at least three days' duration. For the determination of blood sugar Benedict's [8] modification of the Lewis-Benedict method was used. Fat and cholesterol were estimated by the method of Bloor,[9] using the Kober instrument for nephelometric and colorimetric comparisons. The urine was examined daily by the usual methods. The results of the analyses and other important data regarding the patients are given in the accompanying tables and charts.

Of the cases studied, it is obvious that those that have been observed the longest period of time can give the most valuable information concerning the disease, both as regards its morbid physiology and its response to treatment. We have the records of thirty patients who have been treated for from two to six weeks and who have had their blood examined from two to eight times.

Keeping in mind the main object of this study, the metabolism of fat, we have attempted to group our cases according to the behavior of the blood lipoids in relation to the changes in the blood sugar level that occur as a result of dietary treatment. While such a classification must of necessity be somewhat arbitrary, it serves the purpose of convenience in studying the cases, and may facilitate comparison of clinical types. After the groups were arranged from purely laboratory data, they were compared from the standpoint of clinical history. There was found to be a resemblance in the previous history, chronicity, severity of disease and prognosis of the cases in the various groups so striking as to suggest true division into distinct types. The classification from laboratory data was made by one of us (N. F. B.) who was unacquainted with the clinical records, while the clinical classification was made independently by the co-worker, unbiased by the judgment on which the first grouping was based. The resemblances referred to will be discussed below.

GROUPING OF CASES

From the standpoint of laboratory findings, our cases seem to fall into the following groups:

(1) Blood fat increases steadily or intermittently, while sugar comes down.

(2) Blood fat parallels blood sugar.

(3) Blood fat stays at practically the same level while blood sugar decreases.

(4) Unclassified, because of insufficient data.

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8. Benedict, S. R.: J. Biol. Chem. **34**:203, 1918.
9. Bloor, W. R.: J. Biol. Chem. **24**:227, 1916; **31**:576, 1917.

TABLE 1.—Analyses of Cases in Group 1

No.	Age	Sex*	Date	Blood Analyses				Urine		Diet					Weight, Lbs.	Remarks
				Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol		Sugar, Gm.	Acetone	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, C.c.	Calories		
						Whole Blood, per Cent.	Plasma, per Cent.									
3168	70	♀	3/19/20†	0.33	1.57	0.417	0.625	45	0	100	70	28	0	1,142	112	Chronic nephritis; edema preceded by arteriosclerosis
			3/27/20	0.21	2.0	0.476	.....	0	0	29	12	6	5	283	107	
			4/ 3/20	0.18	1.2	0.475	0.756	0	0	58	30	25	5	637	105	
			4/13/20	0.20	0.66	0.476	.....	0	0	70	50	30	0	850		
			4/21/20	0.18	1.28	0.330	0.476	0	0	60	50	30	0	850		
			4/24/20	0.17	1.0	0.250	.....	0	0	60	50	30	0			
			6/ 8/20†	0.25	0.57	0.334	0.261	Trace	0	...	...	...	0			
			6/14/20	0.15	0.89	0.220	.....	0	0	...	...	...	0			
2927	58	♂	2/11/20†	0.34	1.0	0.310	.....	233	++	...	...	...	...	.....	125	Severe long-standing case
			2/16/20	0.30	1.74	0.278	.....	61	Trace	40	0	50	5	396	127	
			2/23/20	0.18	1.1	.....	.....	0	Trace	37	6	0	22	356	121	
			2/27/20	0.17	0.77	.....	.....	0	+	40	20	2	30	358	119	
			3/ 8/20	0.15	1.32	.....	.....	0	Trace	55	20	15	37	719	121	
			3/16/20	0.14	0.9	.....	.....	0	0	70	31	20	0	639	119	
3358	61	♂	4/ 6/20†	0.25	0.66	0.238	.....	51	0	...	...	...	...	.....	168	Severe case complicated by diffuse nephritis; obese at onset
			4/13/20	0.12	1.6	0.278	0.333	0	Trace	65	45	30	0	785	166	
			4/22/20	0.16	1.18	0.196	0.303	0	0	83	71	61	0	1,215		
			4/28/20	0.17	1.4	0.231	0.341	0	0	98	78	71	0	1,458	152	
1411	70	♂	3/ 8/20†	0.29	1.06	.....	.....	Trace	....	115	117	60	0	1,753	196	Severe long-standing arteriosclerosis, myocarditis and angina; received high fat diets before treatment
			3/19/20	0.23	1.46	0.238	0.294	0	....	92	100	86	0	1,612		
			3/26/20	0.21	1.2	0.231	0.264	0	....	90	100	75	0	1,560	196	
3984	62	♂	6/ 8/20†	0.42	0.74	0.394	0.508	80	++	...	...	...	...	.....	109	Hereditary, greatly emaciated
			6/14/20	0.22	1.0	0.308	0.635	0	0	18	0	0	12	156		
			6/29/20	0.25	0.87	0.311	.....	12	Faint trace	60	50	15	0	750		
1859	60	♂	3/ 1/20	0.20	0.72	.....	.....	0	0	60	68	68	0	1,124	300	Onset preceded by dose of thyroid extract, hypertension, myocarditis; obese
			3/ 8/20	0.15	1.1	.....	.....	0	0	63	72	81	0	1,222	298	
3061	71	♂	5/ 6/20	0.25	0.77	0.300	0.375	0	0	80	110	70	0	1,585	133	Arteriosclerosis; advanced case
			5/19/20	0.23	1.06	0.275	0.330	0	0	100	80	60	0	1,360	131	
4214	47	♂	5/10/20	0.33	0.90	0.166	.....	Trace	0	...	...	...	0	.....	...	Synovitis, chronic diffuse nephritis, obesity, ulcers of foot exaggerated by influenza
			5/19/20	0.20	1.2	0.187	.....	Trace	+	...	...	...	0			
			5/29/20	0.15	....	.....	.....	0	0	70	70	40	0	1,070		
			7/ 3/20	0.12	0.87	0.186	0.163	0	0	70	70	40	0	1,070		
3645	60	♂	6/ 4/20	0.27	0.77	0.174	0.261	42	0	...	...	...	0	.....	...	Hypertension, myocarditis, arteriosclerosis; alcoholic
			6/17/20	0.21	1.02	0.178	.....	0	Very faint trace	51	41	60	0	815	199	
3925	64	♂	6/ 8/20	0.22	0.60	0.179	0.208	23	Trace	...	...	...	0	.....	...	Necrosis of bone of foot, overweight; high fat diet previous to treatment
			6/12/20	0.15	0.91	0.180	0.256	0	0	65	60	30	0	980	158	
			6/26/20	0.14	0.98	0.182	0.293	0	0	84	80	70	0	1,336		
3985	54	♂	6/ 9/20	0.38	0.67	0.198	0.298	126	0	...	...	...	0	.....	112	Hereditary type; arteriosclerosis, chronic diffuse nephritis, myocarditis and angina
			6/16/20	0.19	0.93	0.231	0.345	0	Trace	35	15	10	0	315	109	
			7/ 6/20	0.19	1.29	0.299	0.406	0	0	85	75	40	9	1,175	113	

* In this column, ♂ indicates male and ♀ female. † On admission

Normal Values: Blood sugar, 0.09 to 0.12 per cent.; total lipoids, 0.4 to 0.7 per cent.; cholesterol, whole blood plasma, 0.160 to 250.

Group 1 (Table 1).—Especially interesting in this group are those cases which show a very marked increase of blood fat with a coincident drop in the blood sugar level at the time of the second blood analysis, soon after the initiation of the treatment. This is seen to a greater or less degree in all cases. After that the fat in some cases continues to rise; in others it falls, sometimes below the level shown in the first analysis. Later, through a series of fluctuations, it tends to return to the original value while the blood agar remains constant or

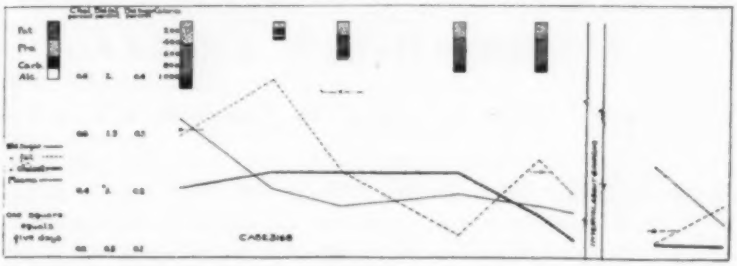

Fig. 1.—Showing behavior of blood lipoids in severe case of diabetes of Group 1. Observed about thirty-five days. Urine sugar on day of first blood analysis 45 gm. Graph on right of chart, readmission about six weeks later.

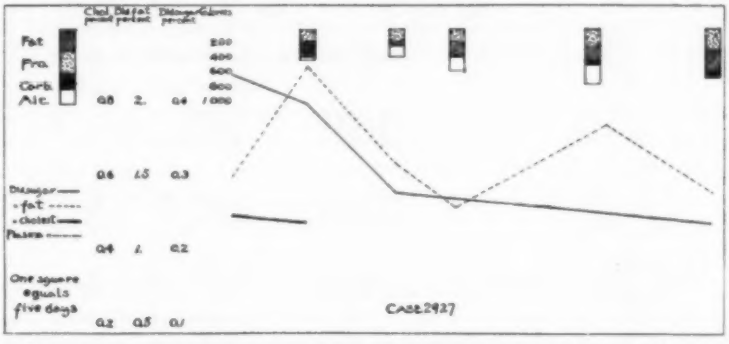

Fig. 2.—Group 1. Sugar in urine on admission 233 gm., blood lipoid value lowest at that time. As sugar excretion diminished lipoids in blood rose. Note absence of fat in diet at the time of most marked hyperlipoidemia.

shows a progressive decline. The cholesterol, both in whole blood and plasma, seems to rise and fall with the blood fat. Case 3168 (Table 1, Fig. 1) is typical of this condition.

The first rise of blood fat occurred during starvation or severe restriction of diet, and was probably due to the mobilization of stored up fat to supply the caloric needs of the body. It is well known

TABLE 2.—Analyses of Cases in Group 2

No.	Age	Sex*	Date	Blood Analyses				Urine		Diet					Weight, Lbs.	Remarks
				Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol		Sugar, Gm.	Acetone	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, C.c.	Calories		
						Whole Blood, per Cent.	Plasma, per Cent.									
2941	65	♂	2/13/20†	0.63	1.56	0.193	.....	56	0	...	...	...	0	.....	164	Necrosis of bone of left great toe; long standing mild case
			2/16/20	0.29	0.82	.....	.....	5	Trace	50	16	45	0	524		
			2/29/20	0.22	0.69	.....	.....	0	0	84	63	40	0	1,063	152	
			3/ 8/20	0.17	0.80	.....	.....	0	0	84	63	40	0	1,063	152	
3042	58	♀	2/28/20	0.22	1.1	.....	.....	7.5	0	111	90	26	0	1,398	122	
			3/ 8/20	0.22	1.3	.....	.....	0	Faint trace	60	44	40	0	764	122	
			4/ 3/20†	0.16	1.1	0.214	.....	0	0	...	...	...	0	.....	117	
3345	61	♀	2/23/20	0.19	1.27	.....	.....	0	Faint trace	70	40	30	0	760	...	Long standing case; mild
			3/ 8/20	0.15	0.83	.....	.....	0	0	70	50	30	0	850		
			4/17/20	0.30	1.3	0.238	0.333	0	0	85	60	35	0	1,020		
3736	46	♂	5/13/20†	0.33	1.0	0.278	0.315	6	Trace	...	...	...	0	.....	139	Hereditary; treated by high fat diet previous to admission
			5/27/20	0.29	0.46	0.158	0.250	Trace	0	...	...	...	0			
			6/ 4/20	0.14	0.86	0.270	0.520	0	Trace	70	50	30	0	770	134	
			6/12/20	0.18	1.1	0.288	0.407	0	0	95	90	70	0	1,470	134	
			6/16/20‡	0.21	0.93	0.299	0.440	0	0	90	90	65	0	1,430		
1181	51	♂	2/16/20†	0.20	0.43	.....	.....	7.5	0	...	...	...	0	.....	179	Hereditary; long standing, mild case
			2/23/20	0.27	0.94	.....	.....	0	Very faint trace	70	80	40	0	1,160	176	
2223	55	♂	3/26/20†	0.26	....	.....	.....	7.5	0	...	...	...	0	.....	205	Infected teeth; long standing mild case
			4/ 7/20	0.17	1.1	0.196	0.278	0	0	85	60	50	0	1,080	195	
			5/12/20†	0.16	0.77	0.167	0.200	0	0	...	...	...	0			
			5/15/20	0.14	0.78	0.204	0.238	0	0	95	75	55	0	1,278	185	
			5/19/20	0.17	1.06	0.214	0.242	0	0	95	75	55	0	1,278		
2807	59	♀	1/22/20†	0.41	....	.....	0.312	96	++	...	...	...	0	.....	87	Angina pectoris; severe case with low tolerance; (diet unreliable)
			2/13/20	0.25	1.1	0.221	.....	0	+	30	12	12	0	276	92	
			2/19/20	0.20	0.89	.....	.....	0	Faint trace	50	12	6	0	332	88	
			2/27/20	0.25	0.80	.....	.....	0	Faint trace	60	20	10	0	400		
			3/19/20†	0.27	0.98	0.203	0.321	0	Very faint trace	26	9	3	0	237	84	
			7/10/20†	0.32	2.0	0.357	0.556	42	0	...	...	...	0			

* In this column, ♂ indicates male and ♀ female. † On admission ‡ Figures for June 16, after meal.

that in fasting the blood lipoids may be increased; this, however, is not constant.[2] Gray [4] found the greatest increase after the second day of fasting, but his figures are not conclusive. Bang [10] was able to produce hyperlipoidemia in fasting dogs in good nutritional condition.

The sharp rise of the fat curve with a corresponding decline in the blood sugar incidental to the sudden withdrawal of carbohydrates from the diet, seems to bear out the suggestion of Joslin, Bloor and Gray [3] and of Bloor,[1] that the lack of these foods is an important element in the production of hyperlipoidemia. The rise seems to be most marked in cases in which the severest cut in carbohydrate allowance was made. The same conclusion with regard to the relationship of carbohydrates to lipoidemia has also been reached by Bang [10] from data obtained in fat feeding experiments on dogs. He found that dogs on a fat rich diet showed, almost invariably, an increase of fat in their blood, which could be prevented by a liberal supply of carbohydrates. He ascribed the appearance of abnormal amounts of fat in the blood to a diminished hepatic function attributable to the lack of sufficient carbohydrates in the circulating body fluids. He claimed that just as the presence of available carbohydrates facilitates the work of the liver in the deaminization of amino acids during protein metabolism, so do these foods increase the functional capacity of that organ to assimilate fats.

Although it appears probable that this rise in blood lipoids coincident with a fall in blood sugar is attributable to the effect of starvation, still it is not impossible that these results may show a metabolic relationship between fats and carbohydrates similar to the relationship which is known to exist between the metabolism of these two substances and the production of acetone bodies in starvation, forced fat feeding, and the acidosis of diabetic coma.

The depression of the fat curve below its initial level (Figs. 1 and 2) sometimes in spite of increased ingestion of fats, would suggest that the "fat pressure" resulting from the preceding increase was sufficient to cause a marked decrease in the blood lipoids by stimulating the fat burning mechanism to increased activity. Fatigue of this mechanism, however, soon sets in, as may be seen from the ensuing rise of the fat curve, even though the diet has not been changed. The source of fat in this second rise is apparently the ingested lipoids and not body fat. Case 2927 (Fig. 2) and Case 3168 (Fig. 1) illustrate this point. An excessive feeding of fat can produce high lipoid values in the blood.[1] In the series of cases presented here this is not shown, because the fat in the diet was controlled by the frequent analyses

10. Bang, I.: Biochem Ztschr. **91**:104, 111, 1918.

TABLE 3.—Analyses of Cases in Group 3

No.	Age	Sex*	Date	Blood Analyses				Urine		Diet					Weight, Lbs.	Remarks
				Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol		Sugar, Gm.	Acetone	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, C.c.	Calories		
						Whole Blood, per Cent.	Plasma, per Cent.									
2926	61	♀	2/18/20†	0.34	1.15	.....	.....	19.8	0	...	...	...	0	.....	163	Preceded by active syphilis
			2/23/20	0.27	1.1	.....	.....	Faint trace	0	58	74	56	0	1,118	159	
			3/ 8/20	0.17	....	.....	.....	0	0	45	64	44	0	902		
			3/19/20	0.20	1.20	0.172	0.198	0	0	46	59	48	0	907		
			3/27/20	0.15	1.2	0.185	0.209	0	0	71	67	58	0	1,119	148	
535	12	♂	3/30/20	0.33	1.4	0.245	.....	16	Faint trace	0	0	0	0	0	57	Onset when 8 years old; studies follow relapse caused by influenza
			4/13/20	0.16	1.3	0.256	0.416	0	Faint trace	50	30	20	0	570	56	
2906	57	♂	3/ 1/20	0.14	0.72	.....	.....	0	Faint trace	95	85	75	0	1,445	173	Complicated by eczema
			5/12/20	0.12	0.71	0.200	0.242	0	0	115	110	90	0	1,810	161	
3863	53	♀	5/27/20†	0.33	0.66	0.250	.....	27	0	...	...	...	0	.....	140	Constipation, obesity
			6/ 4/20	0.12	0.66	0.237	0.348	0	0	81	65	50	0	1,109	136	
			6/12/20	0.16	0.93	0.243	0.327	0	0	75	75	60	0	1,215	135	
3317	66	♂	4/ 3/20†	0.39	....	.....	.....	77	0	...	...	...	0	.....	187	Obesity
			4/ 6/20	0.22	0.90	0.256	.....	25	0	48	12	29	0	416		
			4/13/20	0.14	1.0	0.204	0.278	0	Trace	65	35	20	0	655	192	
3270	21	♂	3/29/20†	0.33	1.5	0.256	0.356	59	—	...	...	...	0	.....	114	Preceded by influenza
			4/ 7/20	0.15	1.3	0.270	0.556	0	0	50	20	16	0	516	117	
			4/17/20	0.12	1.3	0.256	.....	0	0	75	60	40	0	1,000	114	
2604	48	♂	1/10/20	0.13	....	.....	0.250	Trace	Very faint trace	63	65	127	0	1,645	185	Preceded by acute infectious arthritis with necrosis of cartilage of sacro-iliac joint
			1/26/20	0.11	....	.....	0.250	0	0	100	100	100	0	1,700	177	
			5/13/20†	0.16	0.77	0.193	0.193	0	0	...	...	...	0			
			6/ 3/20†	0.14	0.77	0.196	0.196	0	0	...	...	...	0			
3499	15	♀	4/22/20	0.18	1.1	0.278	0.417	Trace	0	28	2	5	0	159	76	Bronzed, anemic
			5/ 3/20	0.13	1.1	0.273	0.469	0	0	50	28	30	0	610	75	
			5/10/20	0.12	1.2	0.288	0.375	0	0	74	45	35	0	481	74	

* In this column, ♂ indicates male and ♀ female. † On admission

of the patient's blood. After the initial fat rise, further increases may indicate excessive ingestion of fat.

Gray [4] found that the lipoid values are higher in a negative than in a positive carbohydrate balance, and still higher in a zero balance. Our figures are not quite in accord with his conclusions, but rather show that in most cases the blood contains the least amount of fat at the time of marked glycosuria, and hence a most decided negative balance.

In addition to the cases that show the changes just discussed, there are some in which the plasma cholesterol behaves in a manner analogous to that of the total lipoids. Since an intimate relationship has been shown to exist between variations in cholesterol and the metabolism of fat,[3, 11] we believe that these cases illustrate the phenomenon

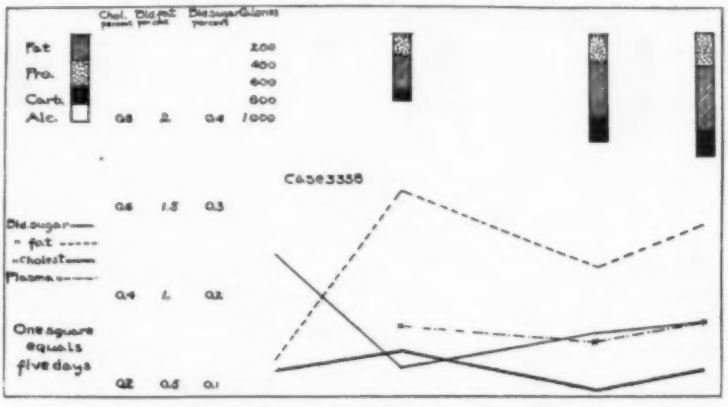

Fig. 3.—Group 1. Blood sugar dropped 50 per cent., while blood fat increased to almost three times its original value. Lipoids did not drop very low after first rise because of relatively high fat and low carbohydrate diet. Whole blood and plasma cholesterol vary with fats. Sugar in urine at the time of admission 51 gm.

of the response of increased lipoids during starvation or low carbohydrate intake. In several cases there is an increase of cholesterol which approximately parallels the increase in total lipoids.

The cases of this group present clinically histories of severe diabetes of long standing, complicated by nephritis, arteriosclerosis, and high blood pressure. They are all cases of true diabetes of low sugar tolerance, and some of the patients are rapidly losing weight. Two patients give a family history of diabetes, and three are obese persons. The prognosis is bad.

11. Hueck, W., and Wacker, L.: Biochem. Ztschr. **100**:84, 1919.

Group 2 (Table 2).—In this group we include those cases in which fluctuations in the blood sugar level are accompanied by similar changes in the concentration of lipoids in the blood during the entire course of treatment. The number of cases that can be properly placed in this group is small, only eight out of twenty-six. It will be noted that, as a rule, the fat comes down more slowly than the blood sugar, while only a slight rise in the blood sugar is sometimes accompanied by a very marked increase in lipoids. Only in one or two instances did the fat fall to a normal level, while the blood sugar, though decreased, remained high. The return of the lipoid value to normal, along with a similar return of the blood sugar, is seen seldom, if ever.

The whole blood cholesterol varies but slightly and in some cases stays constant. The plasma cholesterol is high in most cases and does

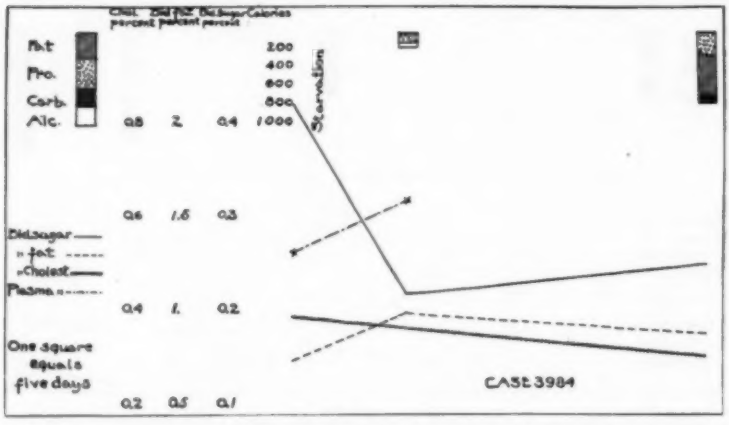

Fig. 4.—Group 1. Case shows lowest lipoid value during marked glycosuria (81 gm. in twenty-four hours) with no carbohydrate intake. Fat does not rise very high because of greatly emaciated condition of patient, and drops again when he reaches an almost zero carbohydrate balance. Plasma cholesterol high and increases markedly during starvation.

not seem to vary exactly with the total lipoids. Cases 2807 and 3223 do not seem to belong in this group. The critical fat determination on the admission specimen is lacking, and we feel that it would have shown that the cases belonged in Group 1.

Cases in Group 2, with the exception of Cases 2807 and 3223, are all characterized by a low grade of diabetes of a long standing. For the most part, the only symptom they exhibit is the frequent appearance of small amounts of sugar in the urine. The patients presented themselves for treatment after many years of neglect to remedy this condition. Most of them have a good sugar tolerance and do not

present a picture of such severe subjective illness as the cases in Group 1. Neither do they appear to get progressively worse as do the members of the first group.

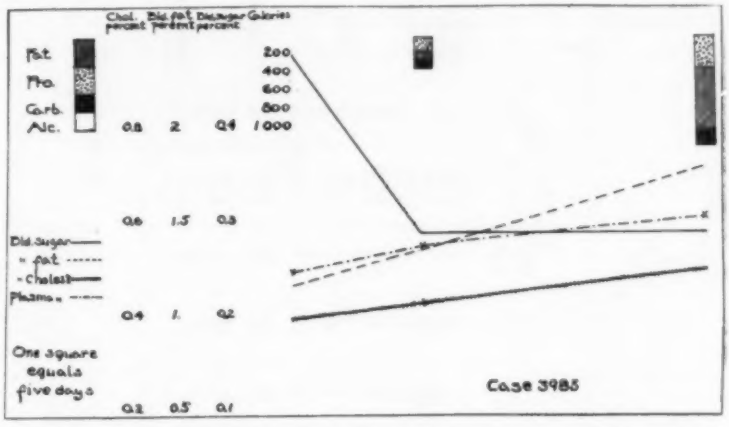

Fig. 5.—Group 1. Blood sugar decreases 50 per cent., maintains a steady high level, while blood fat increases progressively. Whole blood and plasma cholesterol closely parallel blood fat. Sugar in urine on admission 126 gm.

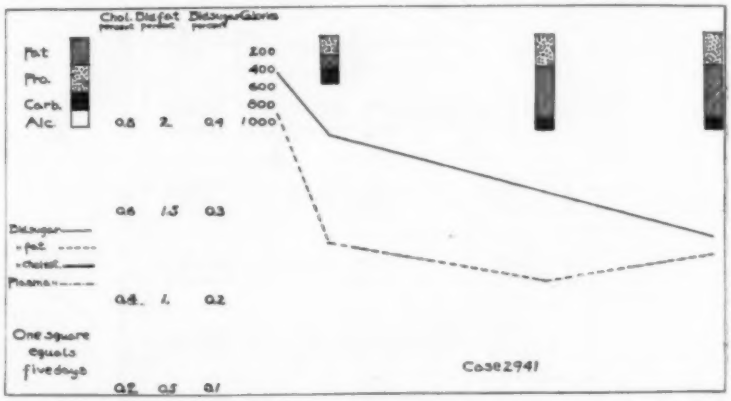

Fig. 6.—Group 2. Quite unlike cases in Group 1, blood fat shows at first an even more decided decrease than blood sugar. Urine sugar dropped from 56 to 5 gm. between first two blood analyses.

Group 3 (Table 3).—This group comprises about 26 per cent. (eight cases) of the cases studied. The fat shows practically no change with either blood or sugar diet. It is usually around 1 per cent.,

TABLE 4.—Analyses of Cases in Group 4

No.	Age	Sex*	Date	Blood Analyses				Urine		Diet					Weight, Lbs.	Remarks
				Sugar, per Cent.	Total Lipoids, per Cent.	Cholesterol		Sugar, Gm.	Acetone	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Alcohol, C.c.	Calories		
						Whole Blood, per Cent.	Plasma, per Cent.									
858	18	♂	12/16/19	0.14	....	.....	0.806	0	0	100	110	100	0	1,780	98	Hereditary type; bronzed leteric skin; diabetes preceded by excessive carbohydrate intake
			1/12/20	0.16	....	.....	0.830	0	Trace	100	110	100	0	1,780	98	
			1/18/20	0.16	....	.....	0.810	0	0	100	110	100	0	1,780		
			1/20/20	0.17	....	.....	0.715	0	0	100	110	100	0	1,780		
			2/ 7/20	0.15	....	.....	0.835	0	0	100	90	70	0	1,490	93	
			5/ 6/20†	0.15	1.35	0.750	1.100	0	0	100	90	70	0	1,490	95	
			6/ 3/20	0.14	0.77	0.652	1.170	0	0	100	90	70	0	1,490	93	
2944	45	♀	1/ 6/20†	0.21	....	.....	.....	Trace	0	...	...	...	0	.....	155	Chronic diffuse nephritis; obesity
			2/ 5/20	0.15	....	.....	0.192	0	0	100	70	70	0	1,310	150	
			2/13/20	0.18	0.43	.....	0.208	0	0	100	80	80	0	1,440	149	
2324	61	♂	12/ 2/19	0.40	....	.....	0.185	41	Trace	...	...	...	0	.....	136	
			12/12/19	0.14	....	.....	0.250	0	Faint trace	90	80	67	0	1,420	134	
			12/19/19	0.14	....	.....	0.355	0	0	100	100	80	0	1,620	134	
2866	58	♀	2/ 6/20	0 13	....	.....	0.228	Faint trace	0	68	72	180	0	1,352	154	Ethmoiditis
			2/16/20	0.14	0.68	.....	.....	0	0	55	80	130	0	1,460	147	
3634	57	♀	5/10/20	0.14	1.1	0.214	0.250	0	0	80	60	50	0	1,060	150	
4075	22	♀	6/17/20†	0.32	0.72	0.190	0.217	24	....	...	...	...	0	.....	99	
3674	66	♀	5/13/20	0.17	0.89	0.174	0.226	Trace	0	...	...	...	0	.....	...	Hypertension
1260	54	♂	5/23/20†	0.29	0.79	0.374	0.500	10	0	...	...	...	0	.....	...	Ulcer of leg

* In this column, ♂ indicates male and ♀ female. † On admission

while the blood sugar drops rapidly or decreases progressively to a normal level. The whole blood cholesterol is remarkably constant. The plasma cholesterol is high in only two cases, and in one case it has the same value as that of the whole blood.

Clinically these cases are remarkable because of the fact that most of them gave a history of infection previous to the onset of glycosuria.

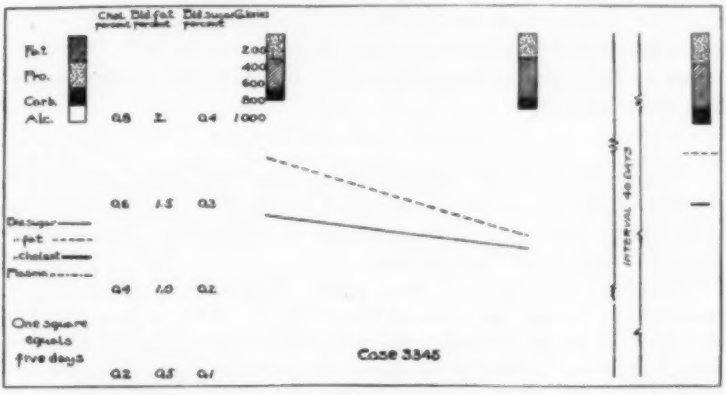

Fig. 7.—Group 2. Plotting of continuous curve of changes in blood constituents not possible because of long interval between last two analyses. Chart illustrates tendency in this patient for blood lipoids to vary with blood sugar.

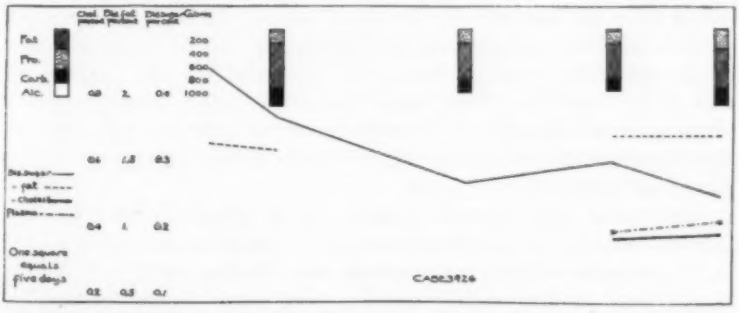

Fig. 8.—Group 3. A representative case of this group. Blood lipoids (four determinations) remain constant while sugar comes down. Sugar in urine on first day of treatment 19.8 gm.

This relationship is so marked as to suggest infection as an etiologic factor or a predisposing influence in these cases. The kinds of infections that figure in this connection are: influenza, syphilis, infection of joints and other infection of undetermined nature.

Group 4 (Table 4).—In the group of unclassified cases, we wish to call attention to Case 858. The patient is a young man, 18 years of age, who has been treated for diabetes for about three years. At first he built up a good tolerance, was getting on well, and his outlook as regards longevity was hopeful. Several months ago we noticed a very marked increase of his plasma cholesterol, which has stayed up ever since and has recently shown a further rise. Since this observation, the tolerance of the patient has gradually diminished, he has lost weight, and now looks bronzed and is very anemic. This case seems to illustrate the prognostic value of cholesterol determinations in diabetic blood.

SUMMARY AND CONCLUSIONS

Twenty-six cases of diabetes under treatment were compared in relation of the blood fat to the blood sugar and were found to fall roughly into three groups, the members of each group bearing certain clinical resemblances to each other.

About 42 per cent. of these cases showed, at the beginning of treatment, a marked increase of blood lipoids, along with a considerable drop of the blood sugar due to starvation or a severely restricted diet. This rise in the lipoid curve must not be taken as a measure of the degree of impairment of the fat burning mechanism; it may be due to a normal response to fasting and also to an insufficient carbohydrate intake. Clinically these were all severe cases of diabetes. Blood fats seemed to rise and fall with the blood sugar in almost 27 per cent. of the cases, decrease in the fat apparently progressing more slowly than the decrease in the blood sugar. All but two of these patients were in a milder stage of the disease. In about 31 per cent. of the cases there was an almost constant value for blood lipoids, at high level, while the blood sugar decreased. They all presented a history of infection previous to the onset of diabetes, and suffered from a somewhat more severe form of the disease than those of the preceding group.

The lipoid value seemed to be lowest in a negative carbohydrate balance, showing that the diabetic organism can utilize fats more readily in the presence of large amounts of sugar in the body, and that in "sugar free" patients there must be a great strain on the fat burning mechanism when large amounts of fats are fed. Evidence of this may often be seen in the high values for plasma cholesterol.

Acknowledgment is due to Mr. Roger S. Hubbard for valuable suggestions.

SOME VARIATIONS IN NORMAL BLOOD SUGAR *

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I

INTRODUCTION

The effect of diet on the blood sugar of normal individuals was reported by Jacobson [1] in 1913 and by Strouse [2] in 1915. Bang's monograph [3] appeared in 1913 and contains a full discussion of blood sugar, both normal and pathologic. Since 1915, as a result of the perfection of chemical methods easily adaptable to the clinical laboratory, the study of blood sugar has become a clinical procedure. All methods in common use report results in grams per 100 c.c. of total blood or blood plasma; and a large collection of valuable data has resulted, especially in regard to diabetes mellitus and to other pathologic states.

Not a great deal of attention has been directed to normal variations, although present methods are so simple that studies of the same individual for a long period of time are easily performed. "Normal" values vary from 0.06 to 0.10 or 0.12 per cent., and it is generally accepted that the most important factor varying the normal is the food factor; carbohydrates having a definite effect on circulating blood sugar, protein and fat having no effect (Jacobson and Edwards [4]). Williams and Humphrey [5] studied thirty-nine young adults, for whom they found an average blood sugar of 0.11, with a range of 0.07 to 0.15. The examinations were made at intervals of from one to six hours after the previous meal, and as a group there was no well marked relationship between the time of eating and the blood sugar level. Apparently these investigators did not attempt to study the diurnal variations of the same individual. Epstein [6] published a long series of observations in which he attempted to prove that the percentage method of recording blood sugar was inaccurate. He believed that the actual amount of circulating blood sugar depended to a great

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* From the Medical Clinic and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital.

1. Jacobson, A. Th. B.: Biochem. Ztschr. **56**:471, 1913.
2. Strouse, S.; Stein, I. F., and Wiseley, A.: Johns Hopkins Hosp. Bull. **26**:211, 1915.
3. Bang, I.: Der Blutzucker, Wiesbaden, 1913.
4. Jacobson, A. Th. B., and Edwards, H.: Am. J. M. Sc. **159**:833, 1920.
5. Williams, J. R., and Humphreys, E. M.: Arch. Int. Med. **23**:537 (April) 1919.
6. Epstein, A. A.: Studies on Hyperglycemia in Relation to Glycosuria, New York, 1916.

extent on the blood volume, which he determined by the hematocrit method. Woodyatt [7] also is of the belief that "in interpreting blood sugar percentages there should be a correction for blood volume, or more exactly for the blood surface at the time of the blood sugar determination."

It would seem possible by a direct method of attack to learn something about normal variations as well as about the value of the percentage method of determining blood sugar. Epstein's criticism of the percentile method is based on the physiologic assumption that changes in blood volume occur after such things as diuresis, sweating, excessive intake of water, or catharsis. Woodyatt [7] could vary blood sugar in his injection experiments by varying the amount of water injected, although the development of glycosuria depended entirely on the velocity and the amount of sugar injected regardless of water intake. It would seem that if the physiologic stimuli which theoretically change blood volume are actually of importance in blood sugar determinations, it should be possible by varying such stimuli to change the blood volume and also the blood sugar percentage. Therefore, the addition of large amounts of water to the intake of a normal individual, or the elimination of water by profuse catharsis should be demonstrable in blood sugar readings, if such physiologic stimuli change the blood volume, and if such changes in the blood volume actually affect blood sugar percentage.

EXPERIMENTAL DATA

Five perfectly healthy young men and women were used as subjects. Blood was taken from each person at the same time each day: Subject 1, at 9 a. m.; Subject 2, at 9:15 a. m.; Subject 3, at 10:15 a. m.; Subject 4, at 11:15 a. m., and Subject 5, at noon. Breakfast for each person was the same daily, except when the nature of the experiment caused a change, which will be noted in the protocols. The breakfasts were as follows:

Subject 1.—Miss B. One roll; 1 cup coffee with sugar.

Subject 2.—Miss L. One piece toast; 1 glass milk.

Subject 3.—Miss E. One piece toast; ½ cantaloupe or other fruit; 1 cup coffee.

Subject 4.—J. K. One cup coffee; 1 glass water; 1 dish oatmeal.

Subject 5.—S. One cup coffee; cream and sugar; fruit; cereal with cream and sugar; 1 egg; a piece toast.

Four of the subjects were workers in the laboratory, doing practically the same kind of work each day. The fifth subject was a

7. Woodyatt, R. T.: Proc. Am. Soc. Clin. Investigation, 1919. (Reprinted from J. A. M. A. **73**:637 [Aug. 23] 1919.)

physician whose daily expenditure of energy was inconstant. By taking blood from each individual at the same time each day and by keeping breakfast constant, the food variation of the individual blood sugar is thereby controlled.

The Lewis-Benedict [8] method was used entirely. In earlier experiments many duplicate determinations were made, comparing the Lewis-Benedict with the modification of the Bertrand, first used by us (Strouse [2]) or with the original Folin-Wu [9] method. It was found that the Lewis-Benedict method gave the most constant and reliable results, and in this and subsequent work it has been the sole method employed. The same technician made all of the determinations. A slight modification in the method of obtaining the blood was adopted, which has simplified, without impairing the accuracy of the procedure. A carefully calibrated and standardized syringe of the tuberculin type was used to withdraw blood from an arm vein by means of a small hypodermic needle. Exactly 2 c.c. was obtained and immediately placed in a 25 c.c. volumetric flask containing distilled water and 3 per cent. sodium fluorid. The saturated picric acid was added and then the method was proceeded with as described by Lewis and Benedict.

EXPERIMENT 1.—July 21 and 22, 1919, the blood sugar of the five normal persons was estimated under constant conditions. July 23, Subject 3 took a large dose of magnesium citrate. July 24, Subject 1 added one glass of water to breakfast. Subjects 2 and 4 added three glasses of water. Subject 3 made no change. Subject 5 took no water, although for the preceding days he had drunk freely all through the morning. The results of this experiment are shown in Table 1.

TABLE 1.—BLOOD SUGAR DETERMINATIONS ON FIVE NORMAL PERSONS UNDER CERTAIN CONDITIONS

Subject	No.	Sex*	Age	Time, a. m.	Blood Sugar			
					July 21, 1919	July 22, 1919	July 23, 1919	July 24, 1919
T. B.	1	♀	[illegible]	9:00	0.06	0.095	0.07	0.07
L. L.	2	♀	23	9:15	0.084	0.084	0.068	0.065
H. E.	3	♀	27	10:15	0.088	0.085	0.066	0.057
J. K.	4	♂	38	11:00	0.081	0.078	0.066	0.063
S. S.	5	♂	37	12:00	.....	0.098	0.065	0.07
Average					0.082	0.086	0.064	0.065

* In this column ♂ indicates male, and ♀ female.

Study of the individual reaction shows that none of the efforts to change blood concentration have any effect on the blood sugar. It is possible, even probable, that changes in blood concentration resulting from such efforts would be evanescent and would have disappeared at the time the blood was taken,

8. Lewis, R. C., and Benedict, S. R.: J. Biol. Chem. **20**:61, 1915.
9. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

just as the ingestion of 100 gm. of glucose by a normal person is demonstrable by increased blood sugar in one-half hour but no longer in an hour. All the figures show a fair uniformity for the first two days with a considerable drop of all on the third and fourth days of the experiment. This phase of the results will be discussed later.

Experiment 2.—Aug. 1 and 2, 1919. No particular attention was paid to any control factor, except the breakfast, which remained constant. As seen in Table 2, *all* of the individuals except Subject 3 show a considerable rise on the second day of the test, although nothing was done to produce such a rise.

TABLE 2.—Blood Sugar Determinations Under Ordinary Conditions

Subject	Blood Sugar	
	Aug. 1, 1919	Aug. 2, 1919
1	0.073	0.091
2	0.061	0.079
3	0.075	0.073
4	0.069	0.084
5	0.067	0.074
Average	0.069	0.08

Experiment 3.—March 4 and 5, 1920. In this experiment again variations in the individual curves occur, at this time the whole group dropping instead of rising as they did in the second experiment. Again no particular effort was made to change either the group or the individual blood sugar.

TABLE 3.—Blood Sugar Determinations Under Ordinary Conditions

Subject	Blood Sugar	
	March 4, 1920	March 5, 1920
1	0.110	0.087
2	0.092	0.072
3	0.10	0.070
4	0.125	0.10
5	0.099	0.096
Average	0.104	0.085

Experiment 4.—March 29 and 30, 1920. This experiment shows less individual and average variation than any of the preceding ones, but the protocol shows that March 29 Subject 5 had taken no water. March 30, Subject 1 took no water all morning. Subject 2 took 1 ounce of magnesium sulphate, with a profuse diarrhea up to the time of the test. Subject 3 made no change. Subject 4 took a full quart of water within the hour before the test. Subject 5 drank fully 2 quarts of water in the course of the morning up to the time of the test. Despite these rather strenuous efforts to change blood concentration, it will be seen that the only variation of any consequence is noted in Subject 3, who had made absolutely no change in her routine on the two days. The average on the second day is lower than the first, and each individual here, as in the preceding experiments, follows the average. Yet in this experiment, the possible changes in water concentration are decidedly greater than in previous experiments. Subjects 1 and 2 made efforts to diminish the water content of the blood; Subjects 4 and 5 made efforts to increase it; and these efforts are certainly in excess of those which might be expected in a normal routine. But these changes in blood volume, if they did occur, are certainly not demonstrable in the blood sugar percentage, which remained nearer a constant level than in previous experiments in which the subjects remained under more constant conditions.

TABLE 4.—Blood Sugar Determinations Under Special Conditions

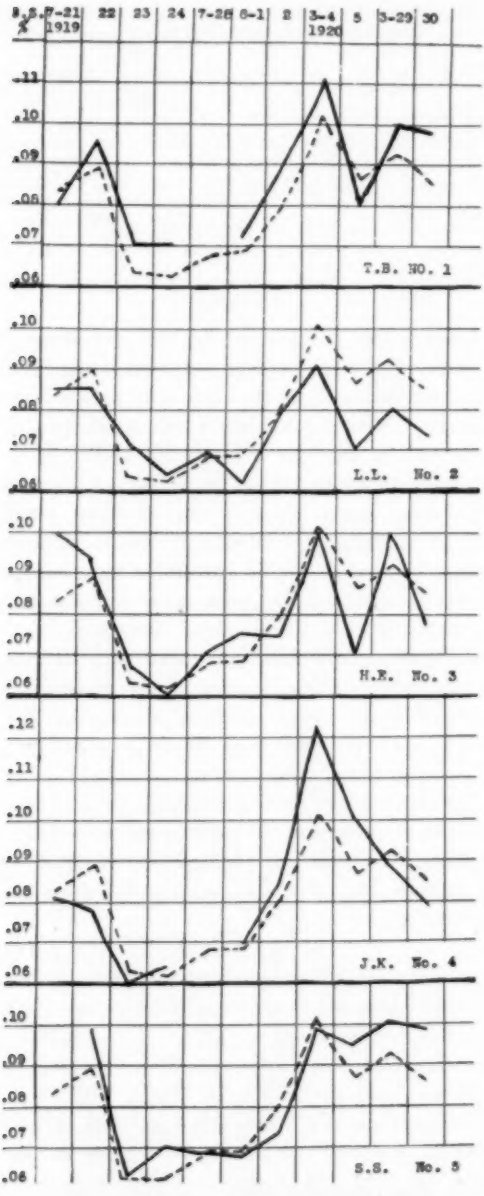
Subject	Blood Sugar	
	March 29, 1920	March 30, 1920
1	0.10	0.099
2	0.06	0.075
3	0.095	0.077
4	0.087	0.077
5	0.10	0.099
Average	0.098	0.085

DISCUSSION

If blood volume can be changed by the procedures used in our experiments, and if the percentage of circulating blood sugar is affected by changes in blood volume, our experiments should demonstrate such changes. Our results clearly indicate that either the physiologic variations of the experiments are not sufficient to change the blood volume or that changes, if they occur, do not alter the percentage of circulating blood sugar. Surely the changes which might be expected to occur in daily life are usually less marked than those of our experiments, so that it seems justifiable to conclude that blood volume need not be considered a necessarily important factor in the usual clinical procedure of blood sugar determination. There is a wide difference between the slight and what may be called the acute changes studied and the chronic pathological disturbances of water balance associated with edema, marked anemia or the desiccation sometimes seen in advanced diabetics. In these pathologic disturbances of water balance the blood volume may, of course, be of importance for a more accurate method of determining blood sugar. Hiller and Mosenthal,[10] from a somewhat different point of attack, have shown that "spontaneous fluctuations in the amount of blood sugar as they occur in the diabetic individual are not paralleled by changes in the water content of the blood."

If, however, we combine the results of all our experiments in the form of a composite chart, plotting the daily blood sugar determinations for each individual as a continuous curve, and paralleling each curve by the average curve of all five individuals, we find some interesting data. It becomes apparent, first, that the average curve of all five persons from July, 1919, to March, 1920, is not a straight line, but it shows variations of from 0.064 to 0.104 per cent.—so-called normal extremes. Second, the average is higher in the cool month of March than in July and August. Third, each individual curve

10. Hiller, A., and Mosenthal, H. O.: J. Biol. Chem. **28**:197, 1916.



Each division represents the blood sugar curve of one normal individual (solid line), paralleled by the curve obtained by averaging all five normals (broken line).

follows the average. In other words, it is seen in studying the blood sugar of the same normal individuals from day to day that, generally speaking, when one changes, all change.

In attempting to explain these variations, we believe that the method of performing the experiments precludes the possibility that either a technical error or any of the control elements of the experiments might be responsible. All determinations were done by the same technician. If the varying controlled factors affected the blood sugar, they should not have done the same thing to all the subjects at the same time. If the protocol of Experiment 4 is studied, it is seen that there is no correlation between the control elements in the experiment and the result. The protocol of Experiment 1 shows that on July 21 and 22 all the blood sugars were higher than on July 23 and 24, and a similar thing is noted in all the other protocols, namely, that *all* are either higher or lower on the second day of the experiment. July 21 and 22 were bright, dry, cheerful days; July 23 and 24 were muggy, hot days, on which a normal person felt disinclined to do more than absolutely necessary work. July 23 and 24 were days on which any kind of effort was difficult as well as distasteful. Might not, then, the lowered blood sugar on these days indicate that there was a lessened expenditure of energy and a consequential lessened call on the energy supply? If there is such a lessened energy expenditure, the most readily available source of energy would probably be the first to show the effect, and the most available source of energy is found in carbohydrates. The changes in blood sugar, then, might be the result of weather influences. Bang [8] reviews the work that has been done on the effect of climatic conditions on blood sugar. Although most of this work has been performed on animals, the collected statistics seem to indicate that climatic conditions may affect the blood sugar. On the other hand, Dexter,[11] in his interesting discussion of weather influences, says that "varying meteorological conditions affect directly, though in different ways, the metabolism of life," and also that "the reserve energy capable of being used for intellectual processes and activities, other than those of the vital organs, is affected most by meteorological changes."

Graham Lusk,[12] discussing the regulation of body temperature, cites experiments proving a direct influence of surrounding temperature and humidity on metabolism, and concludes with the statement "the influence of climate is seen to be noteworthy."

11. Dexter, E. G.: Weather Influences, New York, 1904.
12. Lusk, G.: Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Co., 1917, p. 151.

With the idea in mind that the changes in blood sugar found in our experiments might be the result of weather influences, we attempted to correlate our results with the weather reports. The temperature, humidity, direction and velocity of the wind were studied. We were unable to define any clear relationship between our charts and the weather maps. However, it is known (Dexter) that changes in an individual's reaction to weather conditions may either precede or follow actual changes in the weather. It was the feeling of our experiment subjects that on the days on which they felt more capable of working, the blood sugar readings were higher than on those days on which work was an effort. It is likewise apparent from the charts that the average blood sugar readings were higher in the cooler part of the year (March) than in July. Changes in water concentration resulting from perspiration should make the blood sugar readings higher on the hot days when perspiration is profuse, so that elimination of water through the skin need hardly be considered. Dexter cites instances [13] in which employers of labor do not allow their employees to undertake certain kinds of work when the weather conditions are not suitable.

In conclusion, we suggest, without being able to prove the correctness of the suggestion, that the delicate chemical balance of the body responds to slight stimuli just as readily as it does to greater stimuli. Under certain weather conditions, the body reacts by an unconscious or invisible increase in muscle movements with a resultant increase in energy expense. Under opposite weather conditions, muscle movements are lessened and there is a lessened energy expense. The variations which occur may be slight, but are probably met by variations in the supply of the most easily available source of energy. Carbohydrates are the most easily oxidizable source of energy, and the circulating blood sugar, representing, as it does, the sugar transportation system, may act as an indicator of these slight variations in energy expense.

CONCLUSIONS

1. Efforts to change blood sugar percentage of five normal persons by increased or diminished water intake and excretion failed to change the blood sugar percentage.

2. This indicates that for practical clinical purposes the blood sugar percentage method is accurate.

3. Daily variations of blood sugar percentage occurred in five normal persons. These variations seem to depend on changes in the weather.

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13. Dexter, E. G.: Weather Influences, New York, 1904, p. 239.

OBSERVATIONS ON ALIMENTARY HYPERGLYCEMIA*

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II

Uniformity of methods of procedure of the test for hyperglycemia after glucose ingestion has resulted in rather uniform conclusions regarding the test. Hopkins,[1] Hamman and Hirschman,[2] Janney and Isaacson,[3] Williams and Humphreys[4] showed that the normal individual usually reacted to a given dosage of glucose by a maximum rise in one-half hour and almost immediate drop after the half hour. The maximum rise rarely exceeded 0.16. Bailey[5] reports a normal alimentary glucose test in which the blood sugar in the whole blood was 0.172 in thirty-five minutes, 0.22 in one hour, and 0.216 in one hour and twenty-five minutes after the ingestion of 75 gm. of glucose. This type of curve is considered by most authors as distinctly abnormal, both in regard to the height which it reached and to the length of time it took before returning to normal. The diabetic curve is characterized by a rise at *any* time after the ingestion, a slow descent, and a height depending entirely on the grade of the reaction. There are, however, diabetic curves which closely simulate the normal. Williams and Humphreys,[4] for instance, present two charts (their Nos. 10 and 13) one of which is "practically normal," the other "suggests a very mild, indeed doubtful, diabetes." Yet one of these charts can be superimposed on the other. Hamman and Hirschman have suggested that the test indicated that diabetes represented a quantitative rather than a qualitative difference from the normal.

A review of our own work on this subject for the past few years has shown that there is a definitely normal and definitely pathologic type of reaction, but that between these two extremes the reaction may waver either way. The investigation here reported concerns mainly the interpretion of the wavering type of reaction, its relationship to clinical diagnosis, and its value in the study of the metabolic change in diabetes.

The question as to the blood sugar level at which glycosuria appears, the so-called renal threshold, is one, I believe, which involves consider-

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* From the Medical Clinic and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital.

1. Hopkins, H. H.: Am. J. M. Sc. **149**:254, 1915.
2. Hamman, L., and Hirschman, I. I.: Arch. Int. Med. **20**:761 (Dec.) 1917.
3. Janney, N. W., and Isaacson, V. I.: J. A. M. A. **70**:1131 (April 20) 1918.
4. Williams, J. R., and Humphreys, E. M.: Arch. Int. Med. **23**:537 (May) 1919.
5. Bailey, C. V.: Arch. Int. Med. **23**:455 (April) 1918.

ably more than the metabolism or mobilization of sugar. The retention by the blood of other metabolic products, the concentration of such products in the blood, the ability of the kidney to excrete, should be considered when discussing the renal threshold for sugar. This phase of the problem is now receiving study, and discussion of it will therefore be deferred.

THE NORMAL REACTION

The usual technic was employed. One hundred gm. glucose in 300 c.c. lemonade was given at about 8 a. m. on a fasting stomach. Blood sugar was studied by the Lewis-Benedict method [6] just before the ingestion of the glucose, and usually at intervals of 30, 60, 120 and 180 minutes after the dose. The urine was tested synchronously with the blood sugar, and when present in the test is charted in grams per cent. and grams per hour for the period examined. We tested eight normal persons and found the two characteristics of the normal curve to be (1) it reaches its height in one-half hour and descends immediately; (2) the height is not above 0.145 and in our cases averaged 0.108 per cent. The results of all normal tests are shown in Table 1.

TABLE 1.—NORMAL BLOOD SUGAR REACTION AFTER 100 GM. GLUCOSE

Name	Starvation	½ Hour	1 Hour	2 Hours	3 Hours
A.*	.....	0.06	0.06	0.06	0.08
H.	0.083	0.083	0.068	0.055	0.052
B.*	0.060	0.07	0.07	0.05	0.057
L. B.	0.073	0.115	0.083	0.078	0.067
L. D.	0.052	0.11	0.073	0.064	0.073
S. K.	0.060	0.143	0.133	0.117	0.116
F. B.	0.077	0.142	0.133	0.125	.....
O. S.	0.095	0.142	0.125	0.111	0.111
Average	0.076	0.108	0.093	0.083	0.078

* Tests were performed with the Kowarsky method (Strouse) which usually read lower than the Lewis-Benedict method.

DIABETES

As has already been extensively shown, the blood sugar level after the ingestion of glucose by the diabetic may reach almost any height at any time after the ingestion and is very likely to remain high for a considerable period. In contrast to the normal the characteristics of the typical diabetic curve are: (1), height is rarely reached in the first half hour, but usually occurs at the hour or later and descends slowly; (2), it may reach any height. Table 2 shows data of a representative of the severe diabetic type.

6. Strouse, S.: Arch. Int. Med. **26**:751 (Dec.) 1920.

TABLE 2.—Typical Diabetic Curve of Mrs. G., a Diabetic of Many Years' Standing

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:05 a.m.	0.11	0	0	100
8:10 a.m. (50 gm. glucose)				
8:40 a.m.	0.15	0	0	70
9:10 a.m.	0.24	0.4	1.76	220
9:40 a.m.	0.20	0.8	1.92	122
10:10 a.m.	0.20	1.5	2.40	80

In this table it is seen that the height reached in one hour is above 0.145, there is a continued hyperglycemia and the descent does not even start in two hours. A type between the normal and the extreme diabetic was Mr. L., aged 50, of a diabetic family, who himself had occasionally shown traces of sugar but had no symptoms of diabetes (Table 3).

TABLE 3.—Data of G. L.

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:25 a.m.	0.09	0	0	
8:30 a.m. (100 gm. glucose)				
9:00 a.m.	0.105	0	0	17
9:30 a.m.	0.15	1.35	0.450	17
10:30 a.m.	0.13	5.4	3.35	62
11:30 a.m.	0.10	3.0	1.44	48

Table 3 shows its height in the hour and yet it reaches only 0.15. The large amount of glucose excreted, his reaction in daily life to increased carbohydrate intake as well as his family history all point to his having a true diabetes mellitus. Yet the only difference between this patient and the normal is shown by the curve reaching its height in an hour and by the considerable glycosuria. An even milder diabetic is Mr. S., (Table 4), who at the time of the test was sugar free, but who could produce glycosuria at will by dietary indiscretion.

TABLE 4.—Data of Mr. S.

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:10 a.m.	0.08	0	0	
8:15 a.m. (50 gm. glucose)				
8:45 a.m.	0.14	0	0	15
9:15 a.m.	0.12	0	0	15
9:45 a.m.	0.10	0	0	18

Although this man was and still is definitely diabetic, his reaction at this particular time to 50 gm. glucose is in no way distinguishable from the normal reaction to 100 gm.

In states of hyperthyroidism I have curves identical with the diabetic and with the normal (Tables 5 and 6).

TABLE 5.—H. S., Sugar Curve in Hyperthyroidism

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:55 a.m.	0.095	0	0	250
8:00 a.m. (100 gm. glucose)				
8:30 a.m.	0.17	0	0	0
9:00 a.m.	0.22	1.8	0.81	45
10:00 a.m.	0.20	2.2	1.54	70
11:00 a.m.	0.18	3.0	0.24	8

TABLE 6.—F. B., Sugar Curve in Mild Hyperthyroidism

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:35 a.m.	0.077	0	0	21
8:40 a.m. (100 gm. glucose)				
9:20 a.m.	0.142	0	0	0
9:50 a.m.	0.133	0	0	26
10:50 a.m.	0.13	Faint reduction	0.51	45

TABLE 7.—S. R., Sugar Curve in Cirrhosis of Liver (Syphilis)

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:25 a.m.	0.128	0	0	58
7:30 a.m. (100 gm. glucose)				
8:00 a.m.	0.148	0	0	40
8:30 a.m.	0.22	0	0	33
9:30 a.m.	0.308	1.44	1.37	95
10:30 a.m.	0.275	1.22	0.61	50

The curves in cases of cirrhosis of the liver (Table 7), pituitary disease (Table 8), thromboangiitis obliterans (Table 9) and even chronic nephritis (Table 8) are *as far as their blood sugar is concerned* identical with those found for the diabetic.

TABLE 8.—B. R., Sugar Curve in Pituitary Disease and Nephritis

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
7:50 a.m.	0.061	0	0	95
8:00 a.m. (100 gm. glucose)				
8:30 a.m.	0.169	0	0	18
9:00 a.m.	0.183	0	0	21
10:00 a.m.	0.22	0	0	16
11:00 a.m.	0.22	0	0	36

Rohdenburg, Bernhard and Krehbiel [7] originally thought they had found a specific reaction in cancer patients, but in a recent study [8] of many miscellaneous conditions they report that many absolutely similar curves are found in conditions "as widely different as diabetes mellitus, tuberculosis, epithelioma and pregnancy."

TABLE 9.—H. G., SUGAR CURVE IN THROMBOANGIITIS OBLITERANS

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:30 a.m.	0.111	0	0	0
8:35 a.a.m (100 gm. glucose				
9:05 a.m.	0.181	0	0	46
9:35 a.m.	0.20	0	0	36
10:35 a.m.	0.192	0	0	128
11:35 a.m.	0.111	0	0	90

Whatever the fundamental significance of alimentary hyperglycemia may be, results of the test indicate that the reaction is definitely non specific. The diabetic patient rendered "normal" by treatment may react to 50 or 100 gm. of glucose in exactly the same way as the normal person. Also, other diseases, such as cirrhosis of the liver exophthalmic goiter, chronic arthritis (Pemberton [9]) give "diabetic curves." This lack of specificity between normal and diabetic individuals is quantitative rather than qualitative, at least in regard to sugar mobilization. This suggestion was made by Hamman and Hirschman.[2] Woodyatt,[10] in discussing acidosis in diabetes, says that "the difference between a total diabetic, so-called, and a healthy person is purely relative." If, then, the difference is merely quantitative, it should be possible to feed enough glucose to normal individuals to reproduce at will either the mild or the severe type of diabetic curve. Taylor and Hulton [11] fed 200, 300 and 400 gm. of glucose to normal persons at 10 a. m., after breakfast, and took the blood three hours later. They were unable to show a hyperglycemia at this time, and only an occasional glycosuria. However, by performing the test as outlined, I have been able to vary the reaction of normal persons simply by changing the amount of ingested glucose.

7. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, O.: J. A. M. A. **72**:1528 (May 24) 1919.

8. Rohdenburg, G. L.; Bernhard, A., and Krehbiel, L.: Am. J. M. Sc. **160**: 577, 1920.

9. Pemberton, R., and Foster, G. L.: Arch. Int. Med. **25**:243 (Feb.) 1920.

10. Woodyatt, R. T.: J. A. M. A. **66**:1910 (June 17) 1916.

11. Taylor, A. E., and Hulton, F.: J. Biol. Chem. **25**:173, 1916.

TABLE 10.—Sugar Curve of Mr. M., July 7, 1920

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, Gm. per Cent.
8:10 a.m.	0.10	0
8:15 a.m. (150 gm. glucose)		
8:45 a.m.	0.12	0
9:15 a.m.	0.125	0
10:15 a.m.	0.105	0
11:15 a.m.	0.10	0

The same person, July 9, 1920, received 200 gm. of glucose.

TABLE 11.—Sugar Curve of Mr. M. After Ingesting Glucose July 9, 1920

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.
9:05 a.m.	0.111	0
9:10 a.m. (200 gm. glucose)		
9:40 a.m.	0.143	0
10:10 a.m.	0.154	0
11:10 a.m.	0.119	0
12:10 p.m.	0.10	

His reaction to 200 gm. glucose could be superimposed on Table 3, that of the mild diabetic. With 150 gm. of glucose the reaction is perfectly normal. With 200 gm. it is also normal, except that the height of the curve is reached in one hour and it is slightly above the normal values as we have found them.

Another man, Mr. J., apparently in good health, received 200 gm. glucose July 10, 1920, with the following results:

TABLE 12.—Sugar Curve of Mr. J. After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Quantity Urine, C.c.
8:00 a.m.	0.11	0	0
8:05 a.m. (200 gm. glucose)			
8:35 a.m.	0.20	Trace	115
9:05 a.m.	0.245	Trace	
10:05 a.m.	0.156	Trace	35
11:05 a.m.	0.133	Trace	50

This reaction is definitely diabetic in type, reaching its height in an hour and showing considerable hyperglycemia and very slight glycosuria without a return to the starvation level at the end of three hours.

Another illustration of the lack of type differentiation is seen in the case of Dr. X., who at the time of observation had a boil on the back of his neck. It had been pointed out before (among others by Becker [12] and Strouse [13]) that both furunculosis and carbunculosis are often associated with disturbances of carbohydrate metabolism.

12. Becker: München. med. Wchnschr. **58**:2064, 1911.
13. Strouse, S.: Johns Hopkins Hosp. Bull. **26**:214, 1915.

This subject is a physician who had repeatedly examined his urine for sugar but had never found it present. July 8, 1920, he was given 100 gm. of glucose.

TABLE 13.—Sugar Curve of Dr. X

Time	Blood Sugar, Gm. per Cent.	Sugar in Urine	Quantity Urine, C.c.
9:00 a.m.	0.095	....	0
9:10 a.m. (100 gm. glucose)			
9:40 a.m.	0.143	Trace	100
10:10 a.m.	0.125	Trace	25
11:10 a.m.	0.111	Trace	140
12:10 p.m.	0.111	Trace	45

July 12, 1920, he received 150 gm. glucose in 300 c.c. lemonade.

TABLE 14.—Sugar Curve of Dr. X. After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Sugar in Urine	Quantity Urine, C.c.
9:00 a.m.	0.10	None	55
9:10 a.m. (150 gm. glucose)			
9:40 a.m.	0.175	Trace	17
10:10 a.m.	0.188	Trace	55
11:10 a.m.	0.125	Trace plus	85
12:10 p.m.	0.111	Trace plus	23

It will be seen that the curve of reaction from 100 gm. of glucose is absolutely normal, except for the glycosuria, while from 150 gm. it is diabetic in type, both as regards the time and the height of the curve, reaching a maximum of 0.188 in the hour interval.

These tests clearly indicate that the blood of normal persons differs in reaction to sugar ingestion from the diabetic's only in degree. In the diabetic, if the dose is small enough or the disease mild enough, a normal curve can be obtained. In the normal, if the dose is large enough for the individual, a diabetic curve can be obtained. This curve may belong either to the mild or the severe type as found in diabetes mellitus.

DISCUSSION AND SUMMARY

No discussion of the results found in this work would be complete without reference to the animal experiments reported by Lusk [14] and by Fisher and Wishart.[15] These authors studied the metabolism of the dog after the absorption of dextrose and the effect of such absorption on the composition of the blood. They found that after the ingestion of 50 gm. dextrose in 150 c.c. water there is a rapid absorption of dextrose during the first hour, the sugar in the

14. Lusk, G.: J. Biol. Chem. **13**:27, 1912.
15. Fisher, G., and Wishart, M. B.: J. Biol. Chem. **13**:49, 1912.

blood rises above its normal content, and the hemoglobin content is not profoundly changed. At the end of the second hour, between two-thirds and three-fourths of the sugar has been absorbed, the blood sugar percentage has become normal, and the blood usually is more dilute. The dilution takes place as a result of the increased osmotic power of the blood, due to the increase in sugar content found at the end of the first hour. This condition lasts through the third hour, while during the fourth hour the absorption of dextrose is completed. The urinary secretion suddenly increases, the hydremic plethora tends to diminish, and this hour is the last hour of increased metabolism which has started in the first hour. With the return of the blood to its normal volume, the percentage content of dextrose is not altered through the concentration of the blood. One experiment is reported in which a dog received only 20 gm. of dextrose and the protocol shows a practically complete absorption at the end of the hour with little change in blood volume. With larger amounts than 50 gm. the absorption in the dog is slower and reaction in the blood more prolonged.

These experiments prove conclusively that after giving glucose, the possibility of blood sugar changes being due to changes in blood volume must be taken into account. The dog experiment in which only 20 gm. glucose was given more nearly simulates the test as outlined in this paper; since the giving of 50 gm. dextrose to a 9 kg. dog would be equivalent to giving approximately from 250 to 300 gm. dextrose to a man weighing 50 kg. It is again to be noted that in the dog experiment in which only 20 gm. was given, absorption was complete in one hour and the change in the blood volume was very slight. Bailey [5] in his work attempted to study blood volume, and his charts show only slight changes after the ingestion of 75 gm. dextrose by the normal man.

Although consideration of this work makes it necessary to bear in mind that blood sugar percentage reaction to glucose ingestion may not be an index of disturbed metabolism, it does not interfere, we believe, with certain clinical deductions which can be drawn from the test. Diseases associated with disturbed carbohydrate metabolism do not necessarily present either glycosuria or hyperglycemia as ordinarily understood by the single test. The diabetic may at certain times of the day give a normal blood sugar and show no glycosuria (Mosenthal [16]). In exophthalmic goiter, hyperglycemia is the exception rather than the rule. On the other hand, not all persons showing glycosuria are diabetic. Protocols of my experiments show that the blood sugar

16. Mosenthal, H. O.; Clausen, S. H., and Hiller, A.: Arch. Int. Med. **21**: 93 (Jan.) 1918.

reaction of the diabetic to ingested glucose represents a quantitative rather than a qualitative variation from normal. This reaction is not specific for diabetes, as an identical reaction may be found in a variety of other conditions.

The normal curves reach their height of 0.145 in thirty minutes. The severe diabetic ascended to any height at any time, but rarely before an hour, and dropped to normal slowly. Apparently the first change toward the abnormal is the delay in reaching the height of the curve, as can be seen in the reaction of the mild diabetic, which reached its height in the hour and dropped quickly. Variations from the strictly normal curve suggest a disturbance of sugar mobilization at the time of the test, and this disturbance bears a quantitative relationship to the type of curve presented. At the present time, the reaction cannot be interpreted to mean diabetes or a disturbance of carbohydrate metabolism identical with diabetes, since a similar reaction is found in so many unrelated conditions. Nevertheless, alimentary hyperglycemia has a value in a differential diagnosis in obscure cases—a value entirely nonspecific and relative to other clinical and laboratory data obtained in the individual case.

RENAL GLYCOSURIA *

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III

The diagnosis of renal glycosuria is based on the syndrome of (1) glycosuria without hyperglycemia, (2) glucose excretion almost entirely independent of carbohydrate intake, and (3) absence of diabetic symptoms. To these data should be added, I think, a fourth, namely, that such patients do not subsequently develop diabetes mellitus or show a disturbance of carbohydrate metabolism similar to that found in diabetes mellitus. Not many reported cases have been observed long enough to answer either of the latter two questions. Garrod's [1] case was observed six years, Goto's [2] five years. Allen, Wishart and Smith [3] have recently recorded three cases of renal glycosuria, and have discussed the unsatisfactory nature of this interesting anomaly. It is the purpose of this paper to place on record four cases, patients who have been under observation for from two to eight years since the onset of the disease and on two of whom late metabolic studies were possible.

Glycosuria without hyperglycemia is certainly no longer sufficient evidence on which to base a diagnosis of renal glycosuria, as this combination may be found in patients with mild but true diabetes mellitus. Early cases of diabetes mellitus, those, for instance, discovered in life insurance examination, not infrequently show an excretion of glucose not dependent entirely on carbohydrate intake. In such cases the discovery of glycosuria may precede the onset of typical diabetic symptoms. Study of the cases reported in the literature as renal glycosuria forces the belief that probably not all cases belong to the same class (Strouse and Beifeld [4]). The ultimate outcome or late development in only a few cases is on record. The blood sugar response to ingested glucose has been reported rarely, and the reported results are not entirely uniform. Lewis and Mosenthal [5] record one case with a normal blood sugar curve. Allen, Wishart and Smith [3] say that the low blood sugar values "after large starch or sugar ingestion

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1. Garrod, A. E.: Brit. M. J. **2**:850, 1913.
2. Goto, K.: Arch. Int. Med. **22**:96 (July) 1918.
3. Allen, F. M.; Wishart, M. B., and Smith, L. M.: Arch. Int. Med. **24**:523 (Oct.) 1919.
4. Strouse, S., and Beifeld, A. H.: J. A. M. A. **62**:1301 (April 25) 1914.
5. Lewis, D. S., and Mosenthal, H. O.: Johns Hopkins Hosp. Bull. **27**:133, 1916.

stand in contrast not only to the conditions in diabetes, but also to the hyperglycemia of normal persons after feeding." Yet Paullen's patient [6] showed a blood sugar response to ingested glucose distinctly of the abnormal "metabolic" type. Janney [7] has called attention to the abnormal hyperglycemic curve in Paullen's case. The cases which form the basis of this report shed some light both on the blood sugar reaction and on the clinical course.

REPORT OF CASES

CASE 1.—This man was first seen in December, 1912. He was then 23 years old. He was refused life insurance in November on account of sugar in his urine, which was his reason for consulting us. He had no complaints, no increased appetite, polydypsia or polyuria, and had not lost weight.

Past History.—Five years before he had possibly had typhoid fever. He denied syphilis. He was always a "high liver" and had eaten of rich foods plentifully. He had used alcohol moderately, smoked cigarets freely, and was of a nervous, excitable temperament. About one year before he was in a sleighing accident and was thrown to the street, landing on his head. Unconsciousness lasted only a few minutes, when he arose and drove an automobile home. He had intense headaches for three or five days at that time. He was examined by a competent physician who found no evidence of skull fracture. The urine had been examined shortly before and shortly after the accident but no sugar had been found.

Family History.—There is no diabetes in the family, but all members belong to the high strung, neurotic type.

Examination.—Physical examination (1912) was very thoroughly made and was completely negative. The Wassermann test was negative.

COMMENT

Without going into details on the course of the study made at that time, which has been previously reported [4] it can be said in brief: (1) that he had a glycosuria practically independent of carbohydrate intake; (2) that it was possible to render him sugar free only one time, for a period of a few days; (3) acidosis and clinical signs of acid intoxication developed on carbohydrate withdrawal more quickly than in the normal; (4) restriction of protein intake did not reduce the glycosuria, and (5) the blood sugar both during starvation and after a full meal was normal. (The original blood sugar determinations were from Von Noorden's clinic.) Early in 1913 the patient decided to try to force the issue. If diabetes were present he wanted to know it at once. Consequently he ate anything and everything that he wished and has continued to do so up to the present. He has been under constant observation. At no time has urinary sugar disappeared, and at no time was a hyperglycemia demonstrated in a single examination. In May, 1919, practically seven years after

6. Paullen, J. E.: J. A. M. A. **75**:214 (July 14) 1920.
7. Janney, N. W.: J. A. M. A. **75**:217 (July 14) 1920.

the onset, the patient put himself under closer observation. His history during the past years was that of a perfectly normal man. He had grown stout, had been under no dietary restrictions whatever, and had shown no symptoms of diabetes mellitus. *His urine contained more sugar.* He had been for the past few months indulging in sweets and had been drinking more freely of alcoholic beverages, as he had been acting as official taster of syrups and alcoholic drinks in a big hotel. On May 15, 1919, he was given 100 gm. glucose in 200 c.c. of lemonade, with the results shown in Table 1.

TABLE 1.—SUGAR CURVE OF MR. B. AFTER INGESTION OF GLUCOSE

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:45 a.m.	0.142	3.0	....	120
9:00 a.m. (100 gm. glucose)				
10:00 a.m.	0.27	0	0	0
10:15 a.m.	....	2.8	1.4	75
10:30 a.m.	0.31	0	0	0
11:00 a.m.	0.33	0	0	0
11:30 a.m.	0.36	3.0	2.16	87

TABLE 2.—SUGAR CURVE OF MR. B., AFTER INGESTION OF GLUCOSE, JUNE 6, 1919

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
8:30 a.m.	0.09	0.75	....	28
8:35 a.m. (100 gm. glucose)				
9:05 a.m.	0.10	1.0	0.45	24
9:45 a.m.	....	2.7	2.88	80
10:05 a.m.	0.14	0	0	0
10:35 a.m.	0.10	3.8	4.56	90

This result was extremely surprising. The hyperglycemic curve was definitely diabetic in type (see last article) and the sugar excreted was high. Up to a short time before this test, the amount of sugar excreted had always been so small that quantitative determination by ordinary clinical procedures had been impossible (the new Benedict [8] method was not employed). This sugar gave typical tests for glucose. May 19, 1919, a blood sugar curve taken at 12 noon was 0.05. It was considered possible that the high carbohydrate feeding in the past few months had broken down his tolerance and that the patient had become diabetic. He was requested to refrain from this excessive carbohydrate and alcohol intake but to make no other restrictions in his diet. He returned for a subsequent alimentary test on June 6, 1919, when he was again given 100 gm. glucose in 300 c.c. lemonade.

8. Benedict, S. R.: J. Biol. Chem. **34**:195, 1918.

This test, as far as the blood sugar curve is concerned, is definitely normal except for the delay in reaching its maximum. May 19, 1919, a Mosenthal test meal was given. The meal consisted of 1,760 c.c. fluid—13 gm. nitrogen, 11 gm. salt, 81.25 gm. protein and 162 gm. carbohydrate. The results are shown in Table 3.

TABLE 3.—Reaction of Mr. B. After Mosenthal Test Meal

Time	Quantity Urine, C.c.	Specific Gravity	Sugar, Gm.	Sodium Chlorid, Gm.	Total Nitrogen, Gm.	Urea Nitrogen, Gm.
8-10 a.m.	285	1.018	1.48			
10-12 a.m.	75	1,025	0.50			
12- 2 p.m.	215	1.022	2.41			
2- 4 p.m.	190	1.025	2.41	13.71	8.44	2.51
4- 6 p.m.	145	1.027	0.61			
6- 8 p.m.	145	1,026	0.84			
Total, day	1,055	.....	8.25	13.71	8.44	2.51
8 p.m. to 8 a.m.	350	1.029	2.97	3.57	4.45	1.97
Total	1,405	.....	11.22	17.28	12.89	4.48

This reaction to the Mosenthal test meal is not altogether normal. An excess of sodium chlorid and of nitrogen is excreted, and the urea nitrogen is low. There is no fixation and no retention of total nitrogen. May 20, 1919, the phenolsulphonephthalein test showed in the first hour 23 per cent., and in the second hour 9 per cent., a depression of excretion. As in Allen's three recent cases, the subnormal phthalein excretion is the only indication of any renal retention. Although in our case the test for renal function was done seven years after onset, there seems to be no depression of renal function.

This patient was not seen again until the summer of 1920. July 20, 1920, he was given 100 gm. glucose in 300 c.c. lemonade, with the results shown in Table 4.

TABLE 4.—Sugar Curve of Mr. B., July 20, 1920, After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
9:00 a.m.	0.10	0.41	....	90
9:10 a.m. (100 gm. glucose)				
9:40 a.m.	0.20	0.81	0.55	50
10:10 a.m.	0.156	1.39	1.388	80
11:10 a.m.	0.142	1.31	1.64	125
12:10 p.m.	0.117	1.91	1.81	95

This reaction, when compared with the reactions discussed in the previous paper, will be seen to be abnormal in type. The maximum rise to 0.20 is higher than seen in our normal controls, although unlike the typical metabolic curves the height is reached in the half hour. However, the maintenance of the level of 0.156 in the hour and the slow drop are strongly suggestive of a metabolic type.

Case 2.—A young man, 13 years of age, was first seen in May, 1916. Sugar had been found in his urine accidentally at that time in the course of a routine urine examination in preparation for tonsillectomy. He had had several attacks of acute tonsillitis and the usual infectious diseases of childhood. He had no symptoms of diabetes. His family history was completely negative.

Physical Examination.—He was an unusually robust young chap, and except for the presence of sugar in the urine the physical examination was completely negative. At the time he was first seen he had been on a carbohydrate free diet for three weeks. Despite the presence of a small amount of urinary sugar his blood sugar was only 0.05.

He was not treated for diabetes but was told to lead a normal life, only omitting sugar and food containing sugar. From this time, May, 1916, to June, 1918, he was watched constantly. Growth and development had been normal; the trace of sugar, too small to measure quantitatively by usual clinical procedures, was constantly present. Several blood sugars were done during this period; these were normal or subnormal.

COMMENT

No symptoms of diabetes have arisen. In June, 1918, he became sugar free and was accepted as a first class life insurance risk. He also was accepted in the Reserve Officers' Training Camp. Since that time he has eaten freely of everything, including candy, sweet drinks and pastries. May 23, 1919, a sugar tolerance test was made; 100 gm. glucose in 300 c.c. lemonade was given (Table 5).

TABLE 5.—Sugar Curve of C. F. After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar	Quantity Urine, C.c.
8:30 a.m.	0.08	0	..
8:35 a.m. (100 gm. glucose)			
9:06 a.m.	0.14	0	82
9:35 a.m.	0.05	0	55
10:05 a.m.	0.05	0	52
11:06 a.m.	0.15	Trace	40

This reaction is perfectly normal, except for the peculiar, unexplained rise of the blood sugar and the glycosuria at the two and one-half hour period. The absence of urinary sugar following the ingestion of 100 gm. of glucose three years after the onset of the disease is a striking feature. Between the date of this test and July, 1920, this young man continued to show perfect development, and during this period had his tonsils removed. He continued to be free of symptoms of diabetes although glycosuria was present more or less constantly. July 18, 1920, he was given 125 gm. glucose in 300 c.c. lemonade (Table 6).

It will be seen from Table 6 that the starvation level of 0.13 is rather higher than it should be even for a normal, and that the height of the blood sugar curve is reached in one-half hour, attaining a height of 0.19 with a slow descent to normal. The quantity of sugar in

the urine is small. This reaction, especially for 125 gm. glucose, cannot be considered pathologic; but it is like the reaction in Case 1, suggestive of a metabolic disturbance. As discussed in the previous paper, there is no specific value in the study of alimentary hyperglycemia nor is there a definitely specific variation from normal. Neither one of the tolerance tests made in 1920 on these two cases, however, can be classified as completely within normal bounds.

TABLE 6.—Sugar Curve of C. F., July 18, 1920, After Ingesting Glucose

Time	Blood Sugar, Gm. per Cent.	Urine Sugar, per Cent.	Urine Sugar, Gm. per Hour	Urine Quantity, C.c.
9:10 a.m.	0.13	0.31	....	55
9:20 a.m. (125 gm. glucose)				
9:50 a.m.	0.19	0.31	0.12	30
10:20 a.m.	0.17	0.38	0.19	25
11:20 a.m.	0.14	0.41	0.12	30
12:20 p.m.	0.13	0.45	0.13	30

Cases 3 and 4.—It is impossible to report extensive investigations on these two patients, but they are added to this report as a matter of record, and because in one the onset was characterized by diabetic symptoms. The patients were twins, aged 11 years, first seen in January, 1918. A few weeks previously the little girl complained of irritation of the genitalia and increased thirst. Urinalysis made by her physician at that time showed sugar. The mother, having recognized that in the past both children had had the same diseases at the same time, had the boy's urine examined and was told sugar was present there, too. Both had normal deliveries with uneventful childhood.

Past History.—Both had chickenpox at the age of 5, measles at 6, and whooping cough at 8. The boy had had several attacks of acute tonsillitis and had had his tonsils removed in 1911. The girl had never had trouble with her throat. Both were heavy eaters, the boy specializing in potatoes and bread while the girl went to extremes on candy, jelly and pastries. There is no history of diabetes in the family history.

Physical Examination.—Examination at the time of the first observation showed two very healthy looking youngsters, both inclined to adiposity. Otherwise the physical examination was negative. The blood and stools were negative. The urine of both children showed a reducing substance in small amounts, which the chemical laboratory reported as glucose.

Owing to the history of increased thirst and genital irritation, these patients were considered diabetics, despite the fact that the only blood sugar made was 0.069 on each one. There seemed to be a relationship between carbohydrate intake and glucose excretion, and it had been exceedingly difficult to render these youngsters sugar free without their developing an acidosis. They were passing on an average of from 1.5 to 3 gm. sugar daily, and after the first week this amount remained fairly constant despite efforts to eliminate the sugar entirely. On semistarvation the sugar excretion rose 100 per cent., to 8 gm., and the quick onset of signs of acidosis made it inadvisable to continue treatment. Both these patients were considered at the time to

be mild diabetics of the familial type, although the low blood sugar and the difficulty of rendering them sugar free should have made us regard them as renal glycosurias even at that time. From January to April, 1918, sugar was constantly present in small amounts, but by that time the youngsters had started a revolution and eaten about what they pleased except sugar. In May, 1918, the blood sugar was 0.08 gm. per cent. No symptoms suggestive of diabetes had arisen. The children had both gained in weight and showed normal physical and mental development. At that time they began to eat everything, including sugar, candy, sweet drinks and pastries. They were not seen often, but in February, 1919, the urine of the boy became sugar free, and early in May, 1919, the girl's urine became sugar free. Both children then left the city and subsequent observation has been impossible. In July, 1920, the mother informed us that both children were perfectly normal in every way but the specimens of urine of both still contained sugar.

SUMMARY

Four cases of renal glycosuria are presented. Two patients have been under observation two years, one patient almost five years, and one patient for eight years. All four still show glycosuria. None shows symptoms of diabetes mellitus. In one, tests for renal function seven years after onset showed no depression of renal function except in regard to phthalein excretion. The two who have been observed the longest show at the end of four and eight years, respectively, a utilization of glucose that cannot be considered strictly normal, one at the end of seven years' observation showing a distinctly pathologic alimentary hyperglycemia. This may indicate the beginning of metabolic disturbance. This study emphasizes the importance of long and continued observation of all patients with this most interesting anomaly.

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